# Exhibit 93, part 5

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# ERIONITE

Erionite was considered by previous IARC Working Groups in 1987 (IARC, 1987a, b). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

## 1. Exposure Data

### 1.1 Identification of the agent

Erionite (CAS Registry No.: 66733-21-9) is a naturally occurring fibrous mineral that belongs to a group of hydrated aluminosilicate minerals called zeolites (NTP, 2004). Its molecular formula is $(Na_2, K_2, Ca, Mg)_{4.5}Al_9Si_{27}O_{72}•27H_2O$) (IARC, 1987a).

### 1.2 Chemical and physical properties of the agent

Erionite is a natural fibrous zeolite, found in certain volcanic tuffs as an environmental contaminant. The basic structure of erionite series minerals is an aluminosilicate tetrahedron ($(Si,Al)O_4$) with oxygen atoms shared between two tetrahedra. Erionite is a 'chain silicate' composed of six tetrahedra on each edge of the unit (NTP, 2004). Although erionite has a similar morphology to that of amphibole asbestos (i.e. it has a chain-like structure), it has different chemical and physical properties (Metintas *et al.*, 1999). Erionite occurs as finely fibrous or wool-like white prismatic crystals, with a hexagonal physical structure, and an internal surface area approximately 20 times larger than that of crocidolite asbestos (IARC, 1987a; Metintas *et al.*, 1999; NTP, 2004). It has a density between 2.02–2.08, and absorbs up to 20% of its weight in water. Its gas absorption, ion exchange, and catalytic properties are highly selective and dependent upon the molecular or ionic size of the sorbed compounds as well as upon the cation content of erionite itself (IARC, 1987a). Erionite is not known to occur in other than fibrous form; however, the detailed morphology of erionite 'bundles' that are composed of many 'fibres' and 'fibrils' enhances its surface-area-to-volume ratio drastically (Dogan *et al.*, 2008).

### 1.3 Use of the agent

Natural zeolites have many commercial uses, most of which are based on the ability of these minerals to selectively absorb molecules from air or liquids. Erionite has been used as a noble-metal-doping catalyst in a hydrocarbon-cracking process, and studied for its use in agricultural applications (i.e. in fertilizers and odour control in livestock production) (IARC, 1987a; NTP, 2004). Erionite-rich blocks were historically quarried in the western United States of America for house-building materials, but this use was considered very minor, and not an

intentional use of erionite itself (IARC, 1987a). Natural erionite has not been mined or marketed for commercial purposes since the late 1980s, and has been replaced by synthetic non-fibrous zeolites (Dogan & Dogan, 2008).

## 1.4 Environmental occurrence

### 1.4.1 Natural occurrence

Zeolite minerals are found as major constituents in numerous sedimentary volcanic tuffs, especially where these have been deposited and altered by the action of saline lake water (either by percolation or immersion). Erionite minerals occur as deposits of prismatic-to-acicular crystals in several different types of rock (e.g. rhyolite tuff), and in a wide range of geological settings. They rarely occur in pure form and are normally associated with other zeolite minerals (e.g. clinoptilolite, clinoptilolite-phillipsite). Erionite occurs as two major morphotypes: a short fibre form (named after the original Greek word for wool), and a long fibre form. When ground to powder, erionite fibres resemble amphibole asbestos fibres morphologically (IARC, 1987a; Dogan & Dogan, 2008).

Deposits of erionite have been recorded in Antarctica, Europe (Austria, the Czech Republic, France, Germany, Italy), Africa (Kenya, United Republic of Tanzania), Asia (the Republic of Korea, Japan), North America (USA, Canada, Mexico), as well as Georgia, Iceland, New Zealand, the Russian Federation, Scotland, and Turkey (Dogan & Dogan, 2008; Ilgren *et al.*, 2008).

The fibre size distribution of erionite from different deposits vary. Turkish erionite from Karain contains a higher proportion (32%) of longer fibres (> 4 μm) than erionite from Oregon, USA (11%) or New Zealand (8%). New Zealand and Oregon erionites contain 2–3% of thicker fibres (> 1 μm), whereas Karain erionite does not contain any such fibres (Ilgren *et al.*, 2008).

## 1.5 Human exposure

### 1.5.1 Exposure of the general population

Most of the non-occupational data on exposure to erionite refers to certain villages of the Cappadocia region, Turkey, where people are exposed to erionite throughout their lives. Erionite deposits in the USA are in remote desert regions where there is no stable population (Dogan *et al.*, 2008).

Dumortier *et al.* (2001) evaluated the fibre burden in bronchoalveolar lavage fluid (BALF) of 16 inhabitants of Tuzköy, an erionite-exposed village in the Cappadocia region of Turkey. All subjects were considered to have environmental exposure to erionite (because they were born in the village and had lived there for 10 years). Their fibre burden was compared to that of subjects with ($n$ = 59) and without ($n$ = 16) environmental exposure to tremolite asbestos. Ferruginous bodies (FBs) and fibres in the BALF were measured and analysed by phase–contrast light and transmission electron microscopy (TEM). FBs were detected by light microscopy in the BALF of 12 subjects; of these, seven had concentrations above 1 FB/mL. The geometric mean concentration of FBs was 1.33 FB/mL (95%CI: 0.35–3.04). In the TEM analysis, erionite accounted for 95.7% of the FBs. Erionite fibres were found in the BALF of all 16 subjects; nine subjects had concentrations higher than 300 f/mL. The mean concentration of erionite fibres in BALF was similar to that of tremolite fibres in subjects with environmental exposure to tremolite. Erionite accounted for 35.6% of fibres longer than 8 μm in BALF. Tremolite, in contrast, accounted for 14.0%. The asbestos fibre concentrations in erionite villagers was not different from that in subjects without environmental exposure to tremolite.

### 1.5.2 Occupational exposure

Historically, occupational exposure occurred from the mining and production of erionite. Erionite has also been reported to be a minor component in some commercial zeolites. Although erionite has not been mined for commercial purposes since the late 1980s, occupational exposure to erionite may still occur during the mining, production, and use of other zeolites (NTP, 2004).

## 2. Cancer in Humans

### 2.1 Pleural and peritoneal mesothelioma

At the end of the 1970s, a very high incidence of pleural mesothelioma was observed in one of the regions of Turkey, in three villages in Cappadocia where erionite was present (Sarihidir, Tuzköy, and Karain). During 1970–87, 108 cases of pleural mesothelioma were recorded in the small village of Karain (604 inhabitants in 1974) – equivalent to an annual incidence of more than 800 cases/100000, that is, about 1000 times the rate observed in the general population of industrialized countries. These cases were responsible for nearly half the deaths reported in this village. In Tuzköy, the annual incidence was estimated at 220 cases/100000. Overall, it was identical for men and women, the ratio of men/women was in the range of 1–2, according to series and village, and the mean age was roughly 50, with a range of 26–75 years (Barış *et al.*, 1978; Simonato *et al.*, 1989). Artvinli & Barış (1979) suggested that the presence of erionite in the soil, road dust and building stones of Tuzköy was probably the cause of the high incidence of mesothelioma, and other respiratory abnormalities. It was estimated that a cumulative yearly dose of 1 f/mL induces a pleural mesothelioma rate of 996/100000 persons–year in erionite villages (Simonato *et al.*, 1989).

Barış & Grandjean (2006) extended the follow-up of the inhabitants of Sarihidir and Karain and another village without known exposure to erionite during 1979–2003. A total of 891 men and women, aged 20 years or older, were included, 230 of them from the village without exposure. During the 23-year follow-up, 372 deaths occurred; 119 of these from mesothelioma, which was the cause of 44.5% of all deaths in the exposed villages. Seventeen patients had peritoneal mesothelioma; the rest had pleural mesothelioma. Only two cases of mesothelioma, one of each type, occurred in the control village—both in women born elsewhere. When standardized to the world population, the pleural mesothelioma incidence was approximately 700 and 200 cases per 100000 people annually in the two exposed villages, respectively, and about 10 cases per 100000 people in the control village.

Other studies were published on a cohort of nearly 100 Karain natives who had emigrated to Sweden from the 1960s onwards. In the first of these, seven cases (four women, three men) of mesothelioma were observed (Özesmi *et al.*, 1990). In a follow-up to 1997 including 162 subjects (87 men and 75 women), Metintas *et al.* (1999) reported 14 (78%) deaths due to mesothelioma among the overall 18 deaths during 1965–97; this proportion was even higher than the proportion found in a Turkish study (49%) (Barış *et al.*, 1996). The fact that the immigrant community was stable, and the diagnoses of mesothelioma were all histopathologically proven, gives strength to the findings. The average annual mesothelioma incidence rates in this cohort were about 135 times higher among the men and 1336 times higher among the women compared with the general population of Sweden during 1965–67. The total observed number of malignant pleural mesotheliomas (eight men and ten women) in this group resulted in a risk (mesothelioma standardized incidence ratio) in the men and women subjects of about 265 and 1992 times higher, respectively, than that of the

Swedish population (Metintas *et al.*, 1999). The men/women ratio of pleural mesothelioma in the cohort (0.8) was different from that of industrialized countries, where mesothelioma mostly occurs due to occupational exposure. Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-07-Table2.1.pdf presents the main results of pleural mesothelioma incidence and mortality in populations exposed to erionite in Cappadocia, Turkey.

Selçuk *et al.* (1992) studied 135 mesothelioma cases in Turkey from erionite ($n$ = 58) and tremolite ($n$ = 77) villages. The clinico-anatomical appearance of the malignancies was similar in subjects exposed to asbestos or erionite fibres, and pleural plaques were observed in all subjects. In both the erionite- and the asbestos-exposed groups, one quarter of the patients were less than 40 years of age, and the mean ages were not significantly different between the two groups (respectively, 46.4 and 49.7 years); the ages of the patients were in the range of 27–67 years in the erionite group and 26–75 years in the asbestos group, suggesting that the latent period was not specific to the type of fibre that patients were exposed to. Men and women were approximately equal in number in the erionite group (men/women ratio: 31:27); and men were the predominant gender in the asbestos group (men/women ratio: 51:26). However, this may be explained in part by referral bias, as populations from the three erionite villages were known as a high-risk group, and the patients were referred as soon as a presumptive diagnosis was made; in contrast, there was no equivalent system of survey in the asbestos villages where patients were not actively surveyed, but were admitted after presentation.

Gulmez *et al.* (2004) retrospectively evaluated 67 patients with mesothelioma observed during 1990–2001 in central Anatolia, Turkey. In 51 patients (76.1%), the mesothelioma was confined to the pleura, in 14 patients it was exclusively peritoneal, and in two patients, it involved both areas. Of the 67 cases, 35 (52.2%) were women; the mean age for all cases was 57.6 years. Environmental exposure to erionite and asbestos was found in 50.7% and 25.4% of the cases, respectively.

Some of the studies of erionite-induced mesothelioma in Turkey could not rely on full diagnosis assessment. X-rays and biopsy histology were available for many cases, but not for all. However, some studies were able to perform full histopathological examinations, such as the Selçuk *et al.* (1992) study, or the Swedish study of Karain emigrants (Özesmi *et al.*, 1990; Metintas *et al.*, 1999), and found associations of the same order of magnitude between erionite exposure and the risk of mesothelioma, giving strong confidence in the Turkish findings.

Some reports suggested that the simian virus 40 (SV40) could act as a co-carcinogen to induce mesothelioma (Carbone *et al.*, 2002). This is a controversial issue; however, this hypothesis can be excluded regarding erionite because SV40 DNA was never found in the specimen of Turkish patients (Emri *et al.*, 2000; Carbone *et al.*, 2007). Based on the fact that not all exposed villagers died from mesothelioma and that some families in erionite villages seemed to be at particularly high risk, the cause of the high incidence of mesothelioma was hypothetically attributed to the interaction of erionite exposure and genetic factors (Carbone *et al.*, 2007). Although it is not possible to exclude some genetic susceptibility, this hypothesis remains largely speculative and is not substantiated by sound data, because all relatives shared the same exposure to erionite since birth, except for some women who came from other villages, and because some mesotheliomas occurred in patients whose parents died from other causes, and vice versa (Barış & Grandjean, 2006).

### 2.2 Other cancers

Barış *et al.* (1996) also studied the cancer-specific mortality in the three Turkish erionite villages of Karain, Tuzköy, and Sarihidir. During 1970–94, 305 deaths were reported in Karain; of these, 177 (58%) were cancers, and included 150 cases (49.2%) of malignant pleural mesothelioma, seven cases (2.3%) of malignant peritoneal mesothelioma, and six (1%) of gastroesophageal carcinoma; four deaths (1.3%) from cancer of the lung included two non-smoking women; there were also three cases (1%) of leukaemia, and six of other malignancies (1.9%). During 1980–94, 519 deaths were reported in Tuzköy and Sarihidir (432 and 87, respectively); of these, 257 were cancers, and included 120 cases of malignant pleural mesothelioma, and 64 cases of malignant peritoneal mesothelioma; 30 patients had "intra-abdominal carcinoma" (according to the authors, some of them might have been peritoneal mesothelioma or ovarian carcinoma), and 14 patients had cancer of the lung (four of whom were non-smoking women); there were five cases of gastroesophageal cancer, five deaths due to leukaemia, and 16 cases of various malignancies including ovarian cancer, mesenchymal tumours, and leiomyosarcoma of the colon. These mortality figures lend some support to the hypothesis that erionite fibres also cause cancer other than mesothelioma and cancer of the lung; however, no statistical comparisons and no mineralogical analyses of the tissues were performed to demonstrate this relationship. Another difficulty is the uncertain validity of diagnoses. Barış & Grandjean (2006) also looked at other cancers in their follow-up of the inhabitants of Sarihidir and Karain, but the small number of these cancers ($n$ = 32, accounting for 9% of the total deaths) precluded a detailed analysis.

### 2.3 Synthesis

Studies of villages in Turkey where inhabitants were exposed from environmental sources from birth as well as the follow-up of a cohort of emigrants from one of the exposed villages in Sweden showed an extremely high incidence of pleural and peritoneal mesothelioma that can be causally associated with erionite exposure. The potency of erionite to induce mesothelioma seems much higher than for any type of asbestos.

## 3. Cancer in Experimental Animals

See Section 3 of the *Monograph* on Asbestos in this volume.

## 4. Other Relevant Data

See Section 4 of the *Monograph* on Asbestos in this volume.

## 5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of erionite. Erionite causes mesothelioma.

There is *sufficient evidence* in experimental animals for the carcinogenicity of erionite.

Erionite is *carcinogenic to humans (Group 1).*

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# LEATHER DUST

Leather dust was considered by previous IARC Working Groups in 1980 and 1987 (IARC, 1981, 1987). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

## 1. Exposure Data

### 1.1 Identification of the agent

Leather is the product obtained by tanning skins and hides by any one of several methods. By convention, the term 'hide' generally refers to the skin-covering of larger animals (cows, steers, horses, buffaloes, etc.), and the term 'skins', to those of smaller animals (calves, sheep, goats, pigs, etc.). Although the physical properties of these different skins vary, their basic chemical, physical, and histological characteristics are similar (IARC, 1981).

### 1.2 Chemical and physical properties of the agent

The skin is mainly composed of proteins, although it also contains lipids, carbohydrates, inorganic salts, and water. From the point of view of leather manufacture, the proteins of the skin are the most important components. These proteins include collagen (constitutes the bulk of the fibrous portion), and reticulin (similar to collagen, but differing in its ability to combine readily with silver salts). Elastin, also a fibrous protein, is present in very small quantities, mainly in the grain area, and to a small extent in the blood vessels. Most of the non-collagenous proteins are removed during pre-tanning operations, which are effectively a means of preparing a matrix of relatively pure collagen fibres that will subsequently be stabilized by tanning (IARC, 1981).

Tanning is any process that renders animal hides or skins imputrescible without impairing their flexibility after drying. The most commonly used tanning agents have been vegetable tannins, and basic chromium (III) sulfate.

The vegetable tannins fall into two broad chemicals groups: hydrolysable tannins and condensed tannins. Condensed tannins are more complex chemical structures, and are more likely to be found in the bark or wood of a tree, whereas the hydrolysable tannins predominate in the leaves and fruits. Hydrolysable tannins are mainly glucosides (i.e. glucose esterified with polyhydroxyl phenyl carboxylic acids, such as gallic and ellagic acids) that readily ferment to release the free acid used in primitive tanning processes to control acidity. The chemistry of condensed tannins is complex, and they have been identified as oligomers containing 4–10 flavonoid units, each containing 4–6 hydroxyl groups. Molecular weights in non-aqueous solvents range from 1000–3000, although measurements in aqueous

**Table 1.1 Leather uses in relation to type of hide or skin**

| Skin origin | Use |
|---|---|
| Cow and steer | Shoe and boot uppers, soles, insoles, linings; patent leather; clothing; work gloves; waist belts; luggage and cases; upholstery; transmission belting; sports goods; packings |
| Calf | Shoe uppers; slippers; handbags; wallets; hat sweatbands; bookbindings |
| Sheep and lamb | Grain and suede clothing; shoe linings; slippers; dress and work gloves; hat sweatbands; bookbindings; novelties |
| Goat and kid | Shoe uppers and linings; dress gloves; clothing; handbags |
| Pig | Shoe suede uppers; dress and work gloves; wallets; fancy leather goods |
| Deer | Dress gloves; moccasins; clothing |
| Horse | Shoe uppers; straps; sports goods |
| Reptile | Shoe uppers; handbags; fancy leather goods |

Compiled by the Working Group

solution suggest aggregation or association to give an effective molecular weight of approximately 10000 (IARC, 1981).

In chrome tanning, the trivalent chromium ions form polynuclear complexes involving, typically, four chromium atoms. Ring structures containing coordinated sulfate and hydroxyl ligands are formed, giving an effective ionic weight of approximately 800. When skins are immersed in a solution of basic chromium (III) sulfate, carboxyl side chains on the collagen enter the coordination sphere of the chromium to form an insoluble complex. This reaction, which invariably involves cross-linking, is the basis of chrome tanning (IARC, 1981).

The composition of leather used in the leather-product industries varies. For example, leather used in shoe manufacture may come from the corium part of hide skin processed during tanning. The composition of crust leather varies depending on the tanning processes (Buljan *et al.*, 2000). The reported chromium (III) levels in dust from chrome-tanned leathers have varied from 0.1% to 4.5% by weight (IARC, 1981). Leather may also contain trace amounts of chromium (VI) formed by oxidation of trivalent chromium during the tanning process. For example, in a Danish study of 43 leather products, 35% ($n = 15$) contained chromium (VI) at levels above the detection limit of 3 mg/kg (Hansen *et al.*, 2002).

## 1.3 Use of the agent

The hides or skins from different animals possess unique physical properties that are inherent to the particular animal or breed of animal, due largely to differences in climate, type of feed, etc., to which the animal is exposed. They are thus used for different specific purposes (Table 1.1). For more detailed descriptions, refer to the previous *IARC Monograph* (IARC, 1981).

## 1.4 Occupational exposure

For detailed descriptions of historical exposures to leather dust and other agents in the workplace, refer to the previous *IARC Monograph* (IARC, 1981).

### *1.4.1 Extent of occupational exposure*

Leather and leather-product industries have moved gradually from the industrialized countries to the developing world. For example, shoe manufacture in the United States of America decreased by more than 90% during 1965–2002, and the largest footwear exporter to the USA was the People's Republic of China (Markkanen & Levenstein, 2004). China produced 40% of all prepared shoes in the world at the end of the last century (Chen & Chan, 1999), and the

number of employees in shoe manufacture in China was estimated to be about 2 million (Wang *et al.*, 2006). It was reported that Asian countries supply over 80% of the footwear traded in the world market, and the largest production comes from China followed by India, Indonesia, Viet Nam, Thailand, and Pakistan (Vachayil, 2007). In several developing countries, large and medium-sized manufacturers and retailers are known to use subcontracting practices, informal employment, and so-called home-based shoe-making. There are no reliable estimates on the informal workforce, but it is assumed to be even higher than in the formal sector (Markkanen & Levenstein, 2004). According to statistics from the International Labor Organization, other major countries producing leather products were Mexico ($n$ = 302000 employees), Brazil ($n$ = 305000), Indonesia ($n$ = 279000), the Russian Federation ($n$ = 190000), and Italy ($n$ = 168000) (ILO, 2004).

Although several million people are working in the leather and leather-product industries, only a fraction are exposed to leather dust and other air contaminants in the workplace. No worldwide estimates of the numbers of workers exposed were available to the Working Group.

### 1.4.2 Levels of occupational exposure

Leather dust concentrations in selected studies published since the previous *IARC Monograph* (IARC, 1981) are presented below.

#### (a) Footwear industry

In a Russian mortality study of 5185 shoe-manufacturing workers employed during 1940–76, Zaridze *et al.* (2001) reported leather dust concentrations in the range of 6.5–12 mg/m$^3$ in the following production departments: cutting, fitting, lasting and making, and finishing. In this factory, leather dust was present as a co-exposure with solvents and chloroprene.

Shoe repairers are exposed to the dusts generated during scouring. In a Finnish study of shoe repairers from 11 shops, the time-weighted average concentrations of dust were in the range of 0.07–1.0 mg/m$^3$ in the vicinity of the roughing, scoring, and finishing machines. The dust concentration depended on the age and type of the machine, and the performance of its local exhaust. Electron-microscopic studies showed that the dust samples collected during the machining of shoes contained leather, polymers, and finishing materials. Several degradation products of polymers were present. Dust was formed mainly during the machining of shoes. Dust samples contained also low concentrations of insoluble chromium (0.10–0.32 μg/m$^3$), and hexavalent chromium (0.01–0.08 μg/m$^3$) (Uuklainen *et al.*, 2002).

In a Polish study, dust concentrations were higher in shoe-repair shops than in shoe manufacture. In the repair shops, the recorded concentration of inhaled dust fraction was in the range of 0.5 mg/m$^3$ (glueing of shoes and soles, zipper exchange, and heel abrasion) to 0.9 mg/m$^3$ (sewing of uppers and scouring of heels), with high short-term (> 1 minute) fluctuations in the range of 0.1–14.6 mg/m$^3$. In the shoe factories, the mean concentration of inhalable particles (sample duration > 8 hours) was in the range of 0.12–0.91 mg/m$^3$, but there were high short-term (> 1 minute) fluctuations in the range of 0.62–6.4 mg/m$^3$ (Stroszejn-Mrowca & Szadkowska-Stańczyk, 2003).

#### (b) Leather-tanning and -processing industry

Dust is produced during several processes in tanning operations: chemical dust can be produced during the loading of hide-tanning drums; and leather dust impregnated with chemicals is produced during some mechanical operations, including buffing (IARC, 1981). Total dust levels (personal and static) measured in three countries were presented in Table 2 of the previous *IARC Monograph* (IARC, 1981).

Personal levels ranged from a low of 0.1 mg/m$^3$ in buffing to a high of 21 mg/m$^3$ in semi-automatic staking (IARC, 1981).

### 1.4.3 Particle size distribution

Leather dusts can contain both fibres and grains; the fibres can vary from 30–1200 µm in length and from 10–30 µm in diameter. Grains are usually < 10 µm in diameter. In several surveys in Italy, more than 50% of the total dust in tanneries were reported with having a particle diameter of < 5 µm (IARC, 1981).

Particle sizes have been measured in the dust generated at various workstations in the shoe trade in Poland. The median particle diameter was about 10 µm, and the proportion of extrathoracic particles which would lodge in the nasal fossae was 35–52%, depending on the occupation (Stroszejn-Mrowca & Szadkowska-Stańczyk, 2003).

### 1.4.4 Exposure to other agents

#### (a) Footwear industry

Appendices 5 and 6 of the previous *IARC Monograph* list the various chemicals which may occur in the footwear industry. Most are different solvents used in adhesives, lacquers or cleaning agents. They include petroleum hydrocarbons, chlorinated hydrocarbons, ketones, esters, and alcohols (IARC, 1981). Benzene was previously widely used as a solvent in the shoe industry, and exposure levels during that period may have been high. For example, in Italy, the estimated concentrations of benzene in one shoe factory during 1939–65 were in the range of 0–92 ppm (300 mg/m$^3$). The highest exposures occurred in 1954–60, and benzene was banned by legislation in Italy in 1965 (Seniori Costantini *et al.*, 2003).

Wang *et al.* (2006) reviewed 182 articles on benzene exposure in the shoemaking industry in China during 1978–2004. In 1979–2001, 65% of the measurements exceeded the national occupational exposure limit (OEL) of 40 mg/m$^3$ (13 ppm), and 20% of these exceeded 500 mg/m$^3$ (154 ppm). Benzene levels above 1000 mg/m$^3$ (308 ppm) were not uncommon, and some were in excess of 4500 mg/m$^3$ (1385 ppm). It was also reported that, in some cases, pure benzene was used during the 1980s. The national OEL was lowered to 6 mg/m$^3$ (2 ppm) in 2002, but only 24% of the reported measurements in 2002–04 were below the OEL. The average benzene levels in 2002–04 were 25.1 mg/m$^3$ (8 ppm) in fitting uppers with soles, and 73.6 mg/m$^3$ (23 ppm) in the making of soles. The tasks where exposure occurred most often were fitting uppers with soles, soles-making, uppers-embedding, and uppers-making. Benzene-based adhesives are now banned in China and the national standard for benzene in adhesives is regulated to be less than 0.5% (Wang *et al.*, 2006).

At a large shoe factory in Tianjin, China, as part of a cross-sectional study, Vermeulen *et al.* (2006) collected dermal, inhalation, and urine samples ($n$ = 113) from 70 subjects performing representative tasks and operations at the plant. Mean airborne concentrations of benzene and toluene were 1.52 (standard deviation (SD) 2.82) and 7.49 (SD 11.60) ppm, respectively.

Historically, many toluene-based adhesives manufactured in China contained about 10–30% of benzene as impurity (Chen & Chan, 1999). Exposure to other solvents varies widely, but the levels in some factories may be high. For example, in Viet Nam the national OEL of toluene 100 mg/m$^3$ (26 ppm) was exceeded by six times or more in different sections of a shoe-manufacturing plant in 1996. The concentration of acetone was 6–18 times the Vietnamese OEL 200 mg/m$^3$ (84 ppm) (Chen & Chan, 1999).

Leather dust may also contain agents originating from the processing of leather in tanneries. Levels of chromium (VI) compounds in leather dust are usually very low (see Section 1.4.2a). Leather dust may also contain dyes. Dyes which have been used in the boot and shoe

industry include seven dyes classified by IARC in Group 2B (*possibly carcinogenic to humans*): CI Acid Red 114 (CAS, 6459-94-5), auramine (CAS, 492-80-8), benzyl violet 4B (CAS, 1694-09-3), Trypan blue (CAS, 72-57-1), Ponceau MX (CAS, 3761-53-3), Ponceau 3R (CAS, 3564-09-8), and Rosaline (CAS, 632-99-5) in Magenta (IARC, 1981).

Other agents that may or may not have occurred in the footwear industry include salts of chlorophenols (preservative of leather), acrylic resins, isocyanates (reactive primers, two-part adhesives), polyurethanes and other polymers (artificial leather), chloroprene (component of polychloroprene latex), and wood dust (making of wooden shoes and models) (IARC, 1981).

*(b) Leather-tanning and -processing industry*

Appendices 5 and 6 of Volume 25 list chemicals that may occur in leather tanning (IARC, 1981).

Exposure to chromium (III) salts or vegetable tannins may occur during the weighing and introduction of chromium salts into rotating drums. Also, small amounts of chromium (VI) may be present. Sodium chlorophenates may be used to prevent the deterioration of leather during tanning, and to protect it from mould. Other possible exposures in the tanyard are sulfuric acid and hydrogen sulfide. If dimethylamine is used in the tanning process, *N*-nitrosodimethylamine may be produced (IARC, 1981).

The use of benzidine-based dyes has been reported in the retanning, colouring, and fat-liquoring departments of the leather-tanning and –processing industry. A wide array of chemical solvents (e.g. tetrachloroethylene, toluene, xylene, methyl ethyl ketone and isopropanol), pigments, and waxes may be used in the finishing departments. Exposure to formaldehyde may also occur (IARC, 1981).

*(c) Other leather-product industries*

Exposures in industries producing leather bags, wallets, suitcases, leather-wearing apparel, harnesses, leather furniture and other miscellaneous leather goods are similar to those that occur in the footwear industry (see Section 1.4.2a).

## 2. Cancer in Humans

The boot and shoe industry was first reviewed in the previous *IARC Monograph* IARC (1981). The then Working Group reviewed the results of case series on cancer of the nasal cavity and paranasal sinuses (referred below as sinonasal cancer), several of which compared the history of exposure among adenocarcinoma cases to other cancer controls. The then *Monograph* Working Group also reviewed the results of case series and case reports of leukaemia, as well as other studies focused on bladder, lymphatic and haematopoietic, oral/pharyngeal, lung, and stomach cancer. The Working Group concluded that "Employment in the boot and shoe industry is causally associated with the development of nasal adenocarcinomas" and that "It is most likely that exposure to leather dust plays a role in the association." The Working Group also concluded that an increased risk for other histological types of nasal cancer "may exist." They also observed that "The occurrence of leukaemia and aplastic anaemia among shoe workers exposed to benzene is well documented." They noted that excesses of bladder cancer were associated with the leather industry, but it was not clear if these could be attributed to shoe workers. They also reported that hypothesis-generating studies had observed excesses associated with cancer of the lung, oral cavity, pharynx, and stomach.

The boot and shoe industry was re-reviewed as part of the previous *IARC Monograph* Supplement 7 (IARC, 1987). In the period

following the publication of Volume 25 several new studies had been published. The Working Group for supplement 7 had access to a new retrospective cohort study, three new proportionate mortality studies, as well as new case–control studies of sinonasal cancer and other cancer sites. The conclusions of the Working Group for Supplement 7 were concordant with those of Volume 25. They also concluded that nasal adenocarcinoma was associated with the boot and shoe industry, and that the highest risk was among those with high exposures to leather dust. They also noted that there was evidence for other types of nasal cancer, and that there was further evidence of an increased risk of leukaemia associated with exposure to benzene in the industry. Mixed evidence that may indicate an excess risk of bladder cancer among shoe workers was also noted. Some associations with lung, oral, pharynx, and stomach cancer as well as kidney cancer and mesothelioma were also observed.

In this *Monograph*, studies published in the time following Supplement 7, as well as others that were not previously considered, are reviewed. Of special note are the retrospective cohort studies. The previously reviewed retrospective cohort study of workers in the boot and shoe industry in three English towns (Pippard & Acheson, 1985) has been updated and the end of follow-up extended to 1991, and the cohort study of Florence shoe workers exposed to benzene (Paci *et al.*, 1989) has also been updated and the follow-up extended to 1991 for a pooled analysis (Fu *et al.*, 1996). A US study of shoe workers focused on exposure to solvents, mostly toluene (Walker *et al.*, 1993), has also been updated (Lehman & Hein, 2006). A Russian study of shoe manufacturing workers focused on exposure to chloroprene has also been published (Bulbulyan *et al.*, 1998). The results of registry-based studies are presented in Table 2.1. Descriptive studies with information based only on death certificates are not included. The methods and results of relevant cohort and related studies are summarized in Table 2.2. Only the most recent results are presented in cases where the cohorts were updated. Also included in Table 2.2 are the methods and results of the previously reported proportionate mortality studies.

The results of relevant case–control studies of sinonasal cancer, including those previously reviewed, are summarized in Table 2.3. Studies of other respiratory cancers are summarized in Table 2.4. Case–control studies of bladder cancer are summarized in Table 2.5. Case–control studies of other cancer sites are summarized in Table 2.6. For case–control studies, only those that assessed the association with boot/shoe workers, the broader category of leather products, or with leather dust are included. Those that explicitly included tannery workers, which have a very different set of exposures, were excluded.

## 2.1 Sinonasal cancer

An unusual high prevalence of sinonasal cancer among boot and shoe or other leather workers observed in case series from the Northamptonshire region of England first cast suspicion on a possible association between the malignancy and the occupation (Acheson *et al.*, 1970a, b; Acheson, 1976). In the period following the previous *IARC Monograph* Supplement 7, case series continued to report cases of sinonasal cancer among workers that had been employed as shoe workers or exposed to leather dust. For example, Barbieri *et al.* (2005) reported that seven of 100 epithelial sinonasal cancer cases in the Province of Brescia, Italy, were exposed to leather dust with an average latency of 44 years. A large French adenocarcinoma case series reported that 11 of 418 cases had been exposed to leather dust, whereas 353 had been exposed to wood dust (Choussy *et al.*, 2008). [The Working Group noted that even though leather workers are the second most frequently reported group in these sinonasal cancer case series, it is difficult to interpret these results without knowing

## Table 2.1 Descriptive and census-based studies

| Reference, location, name of study | Population description | Exposure assessment | Organ site (ICD code) | Exposure and histology | No. of cases/ deaths | RR* (95%CI) *(unless indicated otherwise) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Acheson *et al.* (1970*a*, *b*)<br>Incidence study of nasal cancer in Northamptonshire United Kingdom | Comparison of the estimated rate among boot and shoe trade workers (1953–67) to expected numbers based on rates in the Southern Register Areas of England | Occupational history from medical records and mailed survey or interview | Sinonasal cancer, histologically confirmed carcinomas | Boot & shoe workers | | | Age | |
| | | | | All types | 17 | 8 [NR] | | |
| | | | | Adenocarcinomas | 7 | 35 [NR] | | |
| | | | | Squamous carcinomas | 7 | 4 [NR] | | |
| Acheson *et al.* (1981)<br>Incidence study of nasal cancer in England and Wales United Kingdom | 1602 cases diagnosed 1963–67 from The Office of Population Censuses and Surveys | Cases were categorized by occupation | Nasal cancer (160, 160.2–160.9) | All leather workers | 26 | 4.4[a] | SIR, adjusted for snuff and tobacco | [a]indicates significance at the 0.01 level |
| | | | | Shoe makers & repairers | – | 7.1[a] | | |
| | | | | Cutters, lasters & sewers | – | 4.3[a] | | |
| Acheson *et al.* (1982)<br>Incidence study of nasal cancer in Northamptonshire United Kingdom | Comparison of the estimated rate among boot and shoe trade workers (1953–67) to expected numbers based on rates in Northamptonshire | Occupational history from medical records & mailed survey or interview | Sinonasal cancer | Male boot & shoe workers | | | SIR, adjusted for age | |
| | | | | All types | 27 | 4.8 (3.5–7.9) | | |
| | | | | Adenocarcinomas | 11 | 7.8 (3.7–14.3) | | |
| | | | | Squamous carcinomas | 9 | 3.1 (1.4–5.9) | | |
| | | | | Preparation/ finishing | 21 | 4.5 (2.8–6.8) | | |
| Olsen (1988)<br>Pension fund cancer incidence linkage Denmark | 382 Cases from the Danish Cancer Registry diagnosed 1970–84. Registry records linked with the Danish supplementary Pension fund | Longest held occupation from Pension Fund | Sinonasal cancer (160.0, 160.2–160.9) | Manufacture of leather products and footwear (except wooden shoes) | | | SPIR | SPIR for women not provided |
| | | | | Men | 3 | 12.3 (3.1–33.4) | | |
| | | | | Women | 1 | 0.3 expected | | |

**Table 2.1 (continued)**

| Reference, location, name of study | Population description | Exposure assessment | Organ site (ICD code) | Exposure and histology | No. of cases/ deaths | RR* (95%CI) *(unless indicated otherwise) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Andersen *et al.* (1999)<br>Census cancer incidence linkage Nordic countries | Linkage of 1970 Census with incident cancer cases diagnosed in Denmark (1971–87), Finland (1971–90), Norway (1971–91) and Sweden (1971–89) | Leather and shoe workers | All cancers (140–204) | Men employed in the category of shoe and leather workers in the 1970 census | 1436 | 1.1 (1.0–1.1) | SIR, adjusted for age and calendar period | |
| | | | Stomach (151) | | 92 | 1.0 (0.8–1.3) | | |
| | | | Colon (153) | | 107 | 1.1 (0.9–1.4) | | |
| | | | Rectum (154) | | 80 | 1.1 (0.9–1.4) | | |
| | | | Nose (160) | | 11 | 2.9 (1.5–5.3) | | |
| | | | Larynx (161) | | 25 | 1.1 (0.7–1.6) | | |
| | | | Lung (162) | | 264 | 1.1 (0.9–1.2) | | |
| | | | Kidney (180.0) | | 41 | 0.9 (0.6–1.2) | | |
| | | | Bladder (181) | | 114 | 1.1 (0.9–1.3) | | |
| | | | Acute leukaemia (204.3) | | 12 | 0.9 (0.5–1.6) | | |
| | | | Other leukaemia (204.0–2, 4) | | 22 | 1.0 (0.6–1.5) | | |
| Vasama-Neuvonen et. al. (1999)<br>Census cancer incidence linkage Finland | 892591 occupationally active Finnish women at 1970 Census linked with the Finnish Cancer Registry for incidence of ovarian cancer cases during 1971–95 | Occupations with proportion exposed ≥ 20% exposure to leather dust using FINJEM | Ovary (183) | No exposure to leather dust | | 1.0 (ref) | SIR stratified for birth cohort, follow-up period and social status; adjusted for mean number of children, mean age at first birth and turnover rate | Partial overlap with Andersen *et al.* (1999) |
| | | | | Low (> 0.009 mg/m$^3$) | | 1.3 (1.0–1.8) | | |
| | | | | Medium/high | | no data | | |
| | | | | Occupation: | | | | |
| | | | | Cutter for footwear | 6 | 2.5 (0.9–5.4) | | |
| | | | | Pattern maker; cutter | 27 | 1.7 (1.1–2.5) | | |
| | | | | Tanner, fellmonger, pelt dresser | 3 | 0.8 (0.2–2.3) | | |
| | | | | Leather sewer | 4 | 0.6 (0.2–1.5) | | |

**Table 2.1 (continued)**

| Reference, location, name of study | Population description | Exposure assessment | Organ site (ICD code) | Exposure and histology | No. of cases/ deaths | RR* (95%CI) *(unless indicated otherwise) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Tarvainen *et al.* (2008)<br>Census cancer incidence linkage Finland | All Finns born during 1906–45 (725868 men, 825528 women). Census data linked with the Finnish Cancer Registry 1971–95 | Exposure to leather dust using FINJEM | Mouth and pharynx (exluding the nasopharynx) (140–149) | Shoe makers/ cobblers | 2 | 17.4 (2.1–62.9) | SIR, adjusted for age, calendar period and socioeconomic status. Lag time 10 yr | Partial overlap with Andersen *et al.* (1999) |
| | | | | Leather dust: | | | | |
| | | | | Low (< 5 mg/ $m^3$–yr) | 5 | 0.9 (0.3–2.0) | | |
| | | | | Medium (5–19 mg/$m^3$–yr) | 3 | 1.8 (0.4–5.1) | | |
| | | | | High (20+ mg/ $m^3$–yr) | 0 | 0.0 (0.0–15.6) | | |

CI, confidence interval; FINJEM, Finnish job exposure matrix; NR, not reported; RR, relative risk; SIR, standardized incidence ratio; SPIR, standardized proportionate incidence ratio; yr, year or years

## Table 2.2 Cohort studies of boot and shoe workers

| Reference, location, name of study | Cohort description | Exposure assessment | Organ site (ICD code) | Exposure or Sex | Cases/ deaths | RR (95%CI) SMR | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Decouflé & Walrath (1983)<br>USA | Analysis of 3754 deaths (2144 men, 1610 women) among shoe-manufacturing workers identified using union records. Non-whites and persons of unknown sex, race or age were excluded. Deaths were listed from 1966–77 inclusive as obituaries in union newsletters | None | All cancers (140–209) | Men | 464 | 1.10[a] | PMRs calculated from observed and expected deaths adjusted for age and calendar period | [a] indicates statistical significance at the 0.05 level.<br>No sinonasal cancers observed vs 2.2 expected |
| | | | | Women | 430 | 1.12[a] | | |
| | | | Oral & pharynx (140–149) | Men (women: $n = 0$) | 17 | [1.35] | | |
| | | | Stomach (151) | Men | 25 | [1.15] | | |
| | | | | Women | 19 | [1.43] | | |
| | | | Rectum (154) | Men | 22 | [1.57[a]] | | |
| | | | | Women | 19 | [1.81[a]] | | |
| | | | Liver/gallbladder (155–6) | Men | 14 | [1.82[a]] | | |
| | | | | Women | 17 | [2.02[a]] | | |
| | | | Larynx (161) | Men (women: $n = 1$) | 3 | [0.48] | | |
| | | | Lung (162–163) | Men | 155 | [1.20[a]] | | |
| | | | | Women | 35 | [0.92] | | |
| | | | Bladder (188) | Men | 11 | [0.72] | | |
| | | | | Women | 7 | [1.37] | | |
| | | | Kidney (189) | Men | 6 | [0.61] | | |
| | | | | Women | 6 | [0.98] | | |
| | | | Leukaemia (204–207) | Men | 20 | [1.20] | | |
| | | | | Women | 16 | [1.24] | | |
| Garabrant & Wegman (1984)<br>Massachusetts USA | Analysis of death certificates of 1962 shoe workers (1195 men, 767 women) who died in Brockton, Haverhill or Peabody (Massachusetts) during 1954–74 identified by indication of an occupation in leather or shoe manufacturing on death certificates | None | All cancers (140–209) | Men | 217 | 1.08 | PMRs calculated from observed and expected deaths adjusted for age and calendar period | No sinonasal cancers observed |
| | | | | Women | 131 | 0.95 | | |
| | | | Oral & pharynx (140–149) | Men (women: $n = 0$) | 5 | 0.93 | | |
| | | | Digestive tract (150–159) | Men | 84 | 1.4 (1.1–1.7) | | |
| | | | | Women | 44 | 0.99 | | |
| | | | Stomach (151) | Men | 17 | 1.49 | | |
| | | | | Women | 5 | 0.82 | | |
| | | | Larynx (161) | Men (women: $n = 0$) | 3 | 1.16 | | |
| | | | Lung (162) | Men | 55 | 1.04 | | |
| | | | | Women | 13 | 1.07 | | |

**Table 2.2 (continued)**

| Reference, location, name of study | Cohort description | Exposure assessment | Organ site (ICD code) | Exposure or Sex | Cases/ deaths | RR (95%CI) SMR | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Garabrant & Wegman (1984) (contd.) | | | Bladder (188) | Men | 5 | 0.56 | | |
| | | | | Women | 7 | 2.5 (1.2–5.1) | | |
| | | | Leukaemia (204) | Men | 8 | 0.95 | | |
| | | | | Women | 2 | 0.52 | | |
| Walrath *et al.* (1987) New York State USA | Analysis of 4734 death (3512 men, 1222 women) certificates from employees of one shoe-manufacturing company identified using newspaper obituaries. Deaths occurred during 1960–79 | None | All cancers (140–209) | Men | 689 | 1.09[a] | | [a] indicates statistical significance at the 0.05 level |
| | | | | Women | 274 | 1.08 | | |
| | | | Oral & pharynx (140–149) | Men (women: $n = 1$) | 22 | 1.22 | | |
| | | | Larynx (161) | Men (women: $n = 0$) | 7 | 0.78 | | No sinonasal cancers observed vs 1.9 expected |
| | | | Lung and pleura (162 163) | Men | 163 | 0.93 | | |
| | | | | Women | 18 | 0.84 | | |
| | | | Stomach (151) | Men | 71 | 1.83[a] | | |
| | | | | Women | 14 | 1.28 | | |
| | | | Colon (153) | Men | 100 | 1.53[a] | | |
| | | | | Women | 49 | 1.41[a] | | |
| | | | Rectum (154) | Men | 33 | 1.42[a] | | |
| | | | | Women | 16 | 1.97[a] | | |
| | | | Bone (170) | Men (women: $n = 0$) | 6 | 2.23[a] | | |
| | | | Bladder (188) | Men (women: $n = 1$) | 24 | 0.91 | | |
| | | | Kidney (189) | Men | 16 | 1.16 | | |
| | | | | Women | 5 | 1.17 | | |
| | | | Multiple myeloma (203) | Men | 10 | 1.93[a] | | |
| | | | | Women | 8 | 3.46[a] | | |
| | | | Leukaemia (204–207) | Men | 22 | 0.86 | | |
| | | | | Women | 7 | 0.79 | | |

**Table 2.2 (continued)**

| Reference, location, name of study | Cohort description | Exposure assessment | Organ site (ICD code) | Exposure or Sex | Cases/ deaths | RR (95%CI) SMR | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Fu *et al.* (1996) United Kingdom and Italy | Pooled analysis of 2 updated shoe-manufacturing cohorts. 4215 English (follow-up 1950–91, Pippard & Acheson, 1985) and 2008 Italian (follow-up 1950–90, Paci *et al.*, 1989) shoe workers | Workers classified as exposed to leather dust or solvents based on work history (Italian) or 1939 Census (English) | All causes (001–999) | English cohort | 3314 | 0.8 (0.8–0.8) | SMR, adjusted for sex, age, & calendar period using national rates | High exposure to benzene in the Italian cohort before 1963. Exposure to leather dust in the English cohort in the range of 0.5–7.5 mg/m$^3$ in 1976 |
| | | | | Italian cohort | 333 | 0.9 (0.8–1.0) | | |
| | | | All cancers (140–208) | English cohort | 646 | 0.8 (0.7–0.8) | | |
| | | | | Italian cohort | 127 | 1.2 (1.0–1.4) | | |
| | | | Stomach (151) | English cohort | 77 | 0.7 (0.6–0.9) | | |
| | | | | Italian cohort | 25 | 1.9 (1.2–2.8) | | |
| | | | Colon (153) | English cohort | 57 | 0.9 (0.7–1.2) | | |
| | | | | Italian cohort | 10 | 1.7 (0.8–3.0) | | |
| | | | Rectum (154) | English cohort | 51 | 1.1 (0.8–1.4) | | |
| | | | | Italian cohort | 5 | 1.4 (0.5–3.3) | | |
| | | | Pancreas (157) | English cohort | 25 | 0.7 (0.5–1.0) | | |
| | | | | Italian cohort | 2 | 0.5 (0.1–2.0) | | |
| | | | Nose (160) | English cohort | 12 | 8.1 (4.2–14.1) | | |
| | | | | Probable leather dust | 9 | 11.7 (5.3–22.2) | | |
| | | | | High leather dust | 1 | 25.0 (0.6–139) | | |
| | | | | Probable solvent | 2 | 3.9 (0.5–13.9) | | |
| | | | | High solvent | 0 | 0 | | |
| | | | | Italian cohort | 1 | 13.0 (0.31–70.0) | | |
| | | | | Probably leather dust | 0 | 0.0 | | |
| | | | | High leather dust | 0 | 0.0 | | |
| | | | | Probable solvent | 1 | 20 (0.5–99) | | |
| | | | | High solvent | 1 | 20 (0.5–99) | | |
| | | | Larynx (161) | English cohort | 6 | 0.7 (0.2–1.4) | | |
| | | | | Italian cohort | 2 | 0.7 (0.1–2.5) | | |
| | | | Lung (162) | English cohort | 186 | 0.6 (0.5–0.7) | | |
| | | | | Italian cohort | 24 | 1.0 (0.7–1.5) | | |
| | | | Bone (170) | English cohort | 6 | 2.1 (0.8–4.5) | | |
| | | | | Italian cohort | 0 | 0 | | |
| | | | Bladder (188) | English cohort | 34 | 0.8 (0.6–1.2) | | |
| | | | | Italian cohort | 3 | 0.9 (0.2–2.51) | | |

**Table 2.2 (continued)**

| Reference, location, name of study | Cohort description | Exposure assessment | Organ site (ICD code) | Exposure or Sex | Cases/ deaths | RR (95%CI) SMR | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Fu et al. (1996) (contd.) | | | Kidney (189) | English cohort | 8 | 0.7 (0.3–1.4) | | |
| | | | | Probable leather dust | 5 | 0.9 (0.3–2.0) | | |
| | | | | High leather dust | 1 | 3.1 (0.1–17.4) | | |
| | | | | Probable solvent | 1 | 0.3 (0.01–1.4) | | |
| | | | | High solvent | 0 | 0 | | |
| | | | | Italian cohort | 3 | 2.2 (0.5–6.3) | | |
| | | | | Probable leather dust | 0 | 0 (0–18.5) | | |
| | | | | High leather dust | 0 | 0 (0–92.2) | | |
| | | | | Probable solvent | 3 | 3.5 (0.7–10.3) | | |
| | | | | High solvent | 3 | 4.0 (0.8–11.7) | | |
| | | | Multiple myeloma (203) | English cohort | 7 | 1.0 (0.4–2.1) | | |
| | | | | Probable solvent | 3 | 1.2 (0.2–3.4) | | |
| | | | | High solvent | 1 | 5.3 (0.1–29.3) | | |
| | | | | Italian cohort | 3 | 3.7 (0.8–10.8) | | |
| | | | | Probable solvent | 1 | 2.2 (0.5–12.1) | | |
| | | | | High solvent | 1 | 2.4 (0.6–13.6) | | |
| | | | Leukaemia (204–208) | English cohort | 14 | 0.9 (0.5–1.4) | | |
| | | | | Probable solvent | 4 | 0.7 (0.2–1.8) | | |
| | | | | High solvent | 0 | 0 (0–7.9) | | |
| | | | | Italian cohort | 7 | 2.4 (1.0–5.0) | | |
| | | | | Probable solvent | 4 | 2.5 (0.7–6.4) | | |
| | | | | High solvent | 4 | 2.8 (0.8–7.2) | | |

**Table 2.2 (continued)**

| Reference, location, name of study | Cohort description | Exposure assessment | Organ site (ICD code) | Exposure or Sex | Cases/ deaths | RR (95%CI) SMR | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Bulbulyan *et al.* (1998) Russian Federation | Retrospective study of 5815 Russian shoe-manufacturing workers (4569 women, 616 men) employed for 2 mo during 1940–76, followed from 1979 through 1993. Workers employed in auxiliary departments and management employees were excluded | Exposure categories based on chloroprene industrial hygiene data from 1970s Chloroprene exposure: High, 20 mg/ $m^3$ (with co-exposures of benzene) Medium, 0.4–1 mg/ $m^3$ (with co-exposures of formaldehyde, leather dust) No exposure (with co-exposure of leather dust) | All causes (001–999) | Full cohort | 900 | 1.03 (0.97–1.1) | SMR, adjusted for age and sex using 1992 Moscow rates. RR in dose–response analysis adjusted for sex, age, gender and calendar period | Bladder cancer among men SMR, 2.1 (95%CI: 0.4–6.1) All 5 leukaemia cases in the high chloroprene exposure group employed before 1960 RR, 4.1 (95% CI: 1.1–17), co-exposure to benzene possible |
| | | | | Any chloroprene | 640 | 1.1 (1.0–1.3) | | |
| | | | | Medium chloroprene | 446 | 1.1 (0.9–1.3) | | |
| | | | | High chloroprene | 194 | 1.2 (1.0–1.5) | | |
| | | | All cancers (140–208) | Full cohort | 265 | 1.2 (1.1–1.4) | | |
| | | | | Any chloroprene | 184 | 1.0 (0.8–1.3) | | |
| | | | | Medium chloroprene | 128 | 1.0 (0.8–1.4) | | |
| | | | | High chloroprene | 56 | 1.2 (0.9–1.7) | | |
| | | | Stomach (151) | Full cohort | 48 | 1.2 (0.9–1.6) | | |
| | | | | Any chloroprene | 36 | 1.3 (0.7–2.6) | | |
| | | | | Medium chloroprene | 26 | 1.3 (0.7–2.7) | | |
| | | | | High chloroprene | 10 | 1.3 (0.3–3.1) | | |
| | | | Colon (153) | Full cohort | 21 | 1.1 (0.7–1.7) | | |
| | | | | Any chloroprene | 16 | 1.4 (0.5–3.8) | | |
| | | | | Medium chloroprene | 8 | 0.9 (0.3–2.8) | | |
| | | | | High chloroprene | 8 | 2.6 (0.8–7.9) | | |
| | | | Rectum (154) | Full cohort | 14 | 1.1 (0.6–1.9) | | |
| | | | | Any chloroprene | 8 | 0.7 (0.2–2.0) | | |
| | | | | Medium chloroprene | 6 | 0.7 (0.2–2.3) | | |
| | | | | High chloroprene | 2 | 0.5 (0.1–2.7) | | |
| | | | Liver (155) | Full cohort | 10 | 2.4 (1.1–4.3) | | |
| | | | | Any chloroprene | 9 | 4.2 (0.5–33) | | |
| | | | | Medium chloroprene | 6 | 3.8 (0.5–34) | | |
| | | | | High chloroprene | 3 | 4.9 (0.5–47) | | |

**Table 2.2 (continued)**

| Reference, location, name of study | Cohort description | Exposure assessment | Organ site (ICD code) | Exposure or Sex | Cases/ deaths | RR (95%CI) SMR | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Bulbulyan *et al.* (1998) (contd.) | | | Lung (162) | Full cohort | 31 | 1.4 (0.9–2.0) | | |
| | | | | Any chloroprene | 23 | 0.9 (0.4–2.2) | | |
| | | | | Medium chloroprene | 18 | 0.9 (0.4–2.1) | | |
| | | | | High chloroprene | 5 | 1.1 (0.4–3.5) | | |
| | | | Kidney (189) | Full cohort | 10 | 1.8 (0.9–3.4) | | |
| | | | | Any chloroprene | 9 | 3.8 (0.5–31) | | |
| | | | | Medium chloroprene | 7 | 4.1 (0.5–34) | | |
| | | | | High chloroprene | 2 | 3.3 (0.3–37) | | |
| | | | Leukaemia (204–208) | Full cohort | 13 | 1.9 (1.0–3.3) | | |
| | | | | Any chloroprene | 9 | 1.1 (0.3–3.7) | | |
| | | | | Medium chloroprene | 4 | 0.7 (0.2–2.7) | | |
| | | | | High chloroprene | 5 | 2.2 (0.6–8.4) | | |

**Table 2.2 (continued)**

| Reference, location, name of study | Cohort description | Exposure assessment | Organ site (ICD code) | Exposure or Sex | Cases/ deaths | RR (95%CI) SMR | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Lehman & Hein (2006) USA | Update of Walker *et al.* (1995). An SMR analysis of 7828 shoe-manufacturing workers (2545 men, 5283 women) employed for 1 mo or more during 1940–79 at two Ohio manufacturing plants | Exposure data was based on toluene industrial hygiene data from 1970s. Toluene exposure by duration of employment for specific cancers (< 6 mo, 6 mo–1 yr, 2 yr– < 10 yr, > 10 yr) | All causes (0–999) | Men | 1367 | 1.1 (1.0–1.1) | SMR, adjusted for age and calendar period | Results for sinonasal cancer not reported. Reported 'no evidence of any significant level of exposure to leather dust' Reported 'Benzene was not detected in these surveys and company management asserted that benzene had never been present in the solvents used at either of the plants.' |
| | | | | Women | 1768 | 1.0 (1.0–1.1) | | |
| | | | | Employment: | | | | |
| | | | | 1 mo– < 6 mo | 831 | 1.0 (1.0–1.1) | | |
| | | | | 6 mo –2 yr | 747 | 1.0 (1.0–1.1) | | |
| | | | | 2 yr– < 10 yr | 838 | 1.1 (1.0–1.2) | | |
| | | | | ≥ 10 yr | 719 | 1.0 (1.0–1.1) | | |
| | | | All cancers (140–208) | Men | 314 | 1.1 (1.0–1.2) | | |
| | | | | Women | 482 | 1.0 (0.9–1.1) | | |
| | | | | Employment: | | | | |
| | | | | 1 mo– < 6 mo | 233 | 1.1 (1.0–1.3) | | |
| | | | | 6 mo –2 yr | 202 | 1.1 (0.9–1.2) | | |
| | | | | 2 yr– < 10 yr | 202 | 1.0 (0.9–1.2) | | |
| | | | | ≥ 10 yr | 159 | 0.9 (0.8–1.1) | | |
| | | | Buccal cavity & pharynx (140–149) | Men | 8 | 1.1 (0.5–2.2) | | |
| | | | | Women | 1 | 0.2 (0.0–1.0) | | |
| | | | Stomach (151) | Men | 4 | 0.3 (0.1–0.8) | | |
| | | | | Women | 6 | 0.5 (0.2–1.1) | | |
| | | | Lung (162) | Men | 138 | 1.4 (1.2–1.7) | | |
| | | | | Women | 110 | 1.3 (1.0–1.5) | | |
| | | | | Employment: | | | | |
| | | | | 1 mo– < 6 mo | 75 | 1.5 (1.2–1.9) | | |
| | | | | 6 mo –2 yr | 74 | 1.6 (1.3–2.0) | | |
| | | | | 2 yr– < 10 yr | 52 | 1.1 (0.8–1.5) | | |
| | | | | ≥ 10 yr | 47 | 1.2 (0.9–1.5) | | |
| | | | Bladder (188, 189.3–189.9) | Men | 9 | 1.1 (0.5–2.1) | | |
| | | | | Women | 6 | 1.0 (0.4–2.2 | | |

**Table 2.2 (continued)**

| Reference, location, name of study | Cohort description | Exposure assessment | Organ site (ICD code) | Exposure or Sex | Cases/ deaths | RR (95%CI) SMR | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Lehman & Hein (2006) (contd.) | | | Kidney (189.0–189.2) | Men | 6 | 0.9 (0.3–1.9) | | |
| | | | | Women | 8 | 1.1 (0.5–2.1) | | |
| | | | Leukaemia (204–208) | Men | 8 | 0.7 (0.3 –1.4) | | |
| | | | | Women | 19 | 1.2 (0.7–1.9) | | |
| | | | | Employment: | | | | |
| | | | | 1 mo– < 6 mo | 8 | 1.1 (0.5–2.2) | | |
| | | | | 6 mo–2 yr | 4 | 0.6 (0.2–1.6) | | |
| | | | | 2 yr– < 10 yr | 9 | 1.3 (0.6–2.5) | | |
| | | | | ≥ 10 yr | 6 | 1.0 (0.4–2.2) | | |

CI, confidence interval; mo, month or months; PMR, proportional mortality ratio; RR, relative risk; SMR, standardized mortality ratio; vs, versus; yr, year or years

**Table 2.3 Case–control studies on sinonasal cancer in shoe workers or workers exposed to leather dust**

| Reference, study location and period | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | No. of cases/ deaths | OR (95%CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Casalini *et al.* (1980) Hospital-based Florence, Italy 1963–77 | Nose and paranasal sinuses | 66 cases (46 men, 20 women) diagnosed with adenocarcinoma in Florence, records from the Otorhinolaryngology clinic and the Radiology Insititute of the University of Florence | Controls were matched to cases by sex, age (± 5 yr), place of residence, smoking habits and year of hospital admission. Each case had 2 non-cancer controls admitted to the department of internal medicine in the hospital | Social worker interview to collect data on occupational history | Shoe makers | | Adenocarcinomas 7/11 cases 0/22 controls ($P < 0.001$) | Matched on sex, age, place or residence (as surrogate for SES), smoking habits and year of admission | |
| Hardell *et al.* (1982) Sweden 1970–79 | Nose (ICD 160) | 44 cases, age 25–85 and residents of Southern Sweden reported to the Swedish Cancer Registry 1970–79 | 541 controls referents from another study with the same region, 1970–78 | Work history from mailed questionnaire | Leather work | | 1 case (2.8%) vs 5 controls (0.9%) | | Case was 1 of 3 adenocarcinomas |
| Britton *et al.* (1981) Hospital-based N. Carolina & Virginia, USA 1970–80 | Nasal cavity and sinuses (160.0, 160.2–160.5, 160.8–160.9) | 193 incident cases from 4 hospitals | 2 controls per case matched on age, sex, race, and region. 232 hospital & 140 death certificate controls (deceased cases had 1 living & 1 dead control) | Telephone interview with subject or next-of-kin | Leather or shoe industry<br>Leather exposure | | 1.3 (0.1–9.4)<br>0.7 (0.2–2.0) | Adjusted for sex | |

## Table 2.3 (continued)

| Reference, study location and period | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | No. of cases/ deaths | OR (95%CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Merler *et al.* (1986)<br>Vigevano, Italy<br>1968–82 | Nasal epithelial tumours<br>Nasal adenocarcinomas | 21 cases (16 men, 5 women) from otolaryngology departments of three hospitals, the hospital cancer registry of the National Cancer Institute of Milan and city mortality records | 2 controls per case were selected from the general population and matched by vital status, age, sex and residence | Interview to obtain occupational history. Estimated level of exposure based on specific tasks, workplaces, duration, technology and hygienic evaluation | Light/Uncertain<br>Heavy<br><br>Light/Uncertain<br>Heavy | 7<br>11<br><br>5<br>8 | All epithelial tumours:<br>7.5 (1.8–31.7)<br>121 (17.3–844.3)<br>Adenocarcinoma:<br>20.4 (2.7–152.0)<br>88.0 (12.1–642.0) | Matched on age, sex, and residence | Matched and unmatched analyses yielded similar results. Unmatched results presented |
| Bimbi *et al.* (1988)<br>Hospital-based<br>Milan, Italy<br>1982–85 | Nasal cavity and paranasal sinus (160.0–160.9) (epithelial neoplasms) | 53 (40 men, 13 women) cases admitted to the Head and Neck Oncology Department of the National Institute for Study and Treatment of Cancer in Milan | 217 controls selected from patients admitted in the same yr with malignant tumour of the nasopharynx, thyroid or salivary glands | Occupational history was taken from hospital records | Leather workers (3 cases, 0 controls) | | RR is reported as incalculable because 0 controls reported working in the leather industry | | |
| Loi *et al.* (1989)<br>Hospital-based<br>Pisa, Italy<br>1972–83 | Nasal cavity and paranasal sinus (160.0–160.9) | 38 incident cases (all male) of nasal and paranasal sinus cancer admitted to Pisa University Hospital between October 1972 and October 1983 | 186 hospital controls (5:1 match) matched for sex, age (± 3 yr), province of usual residence, admission date (± 6 mo), excluding nasal tumours, respiratory tract malignancies and lymphomas | Mailed-out questionnaire on employment in leather-working industries & specific occupational risk factors | Leather exposure: All tumours | | 8.1 (2.0–33.5) | Matched on age, sex, and residence | |

**Table 2.3 (continued)**

| Reference, study location and period | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | No. of cases/ deaths | OR (95%CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Shimada *et al.* (1989)<br>Hospital-based<br>Japan<br>1983–85 | Maxillary sinus (160.2), squamous cell carcinomas only | 66 cases aged 42–77 yr (45 men, 21 women) October 1983 to October 1985 six university hospitals in six prefectures | 132 controls were randomly selected from the same jurisdiction as the cases residence and matched for age (± 5 yr) and sex (2:1 match) | Self-administered questionnaires, occupational exposures and other risk factors | Leather workers | | 2.1 (0.1–38.3) | Matched on age and sex | |
| Bolm-Audorff *et al.* (1989, 1990)<br>Hospital-based<br>Hessia, Germany<br>1983–85 | Nasal and paranasal sinus cancer (160) | 62 cases identified through 85 otorhinolaryngogical and 8 pathology departments | Patients with non-occupational bone fractures matched on age, sex, and residence | In-person interviews | Leather dust exposure | | 2/62 cases and 0/62 controls | Matched on age, sex, and residence | |
| Combes *et al.* (1992a)<br>Hospital-based<br>Verona, Vicenza, Siena, Italy<br>1982–87 | Nasal cavity and paranasal sinus (160) (epithelial neoplasms) | 78 cases (55 men, 23 women) from the University of Verona Institute of Pathology and ENT Clinic, ENT departments at the hospitals of Vincenza, Bussolengo, and Legnago and Institute of Pathology at the University of Siena | 254 controls (184 men, 70 women) admitted to the same hospitals (excluding chronic rhinosinusal disease and actute nasal bleeding) matched for admission date, hospital, sex, age (± 5 yr) & residence | Interviews and/or mailed questionnaires collected information on occupational history with specific questions for leather workers | Leather workers<br>Shoe makers<br>Associated with leatherwork:<br>Adenocarcinoma<br>Squamous cell carcinoma | 5 | 6.8 (2.2–15)<br>8.3 (1.9–36)<br><br>14.1 (2.6–76)<br>1.6 (0.21–12) | Matched on age, sex, and residence. 90% confidence limits used | |

**Table 2.3 (continued)**

| Reference, study location and period | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | No. of cases/ deaths | OR (95%CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Comba et al. (1992b) Hospital-based Brescia, Italy 1980–89 | Nasal cavity and paranasal sinus (160) (epithelial neoplasms) | 35 cases diagnosed and treated by the ENT department of the radiotherapy unit of the Brescia Hospital | 102 controls from ENT department and radiotherapy unit files with neoplastic diseases of the head and neck and matched for age (± 5 yr) and sex | Telephone interview to collect detailed occupational history, specific items related to shoe-manufacturing industries | Leather workers (1 case) | | 9.0 | Matched on age and sex | |
| Magnani et al. (1993) Hospital-based Biella, Italy 1976–88 | Nasal cavity and paranasal sinus (160.0, 160.2–160.9) (epithelial or unspecified neoplasms) | 33 cases identified by the Local Health Authorities of Biella and Cossato | 131 controls (4:1 match) randomly chosen and matched on age and sex admitted same hospital, same year | Mailed questionnaire to patient and next-of-kin with work history | Shoe-manufacturing or other leather industries | 3 | 3.5 (0.6–2.–0.3) | Matched on age and sex | |
| Luce et al. (1992, 1993) Population-based France 1986–88 | Nasal cavity and paranasal sinus (160.0, 160.2–160.9) | 207 (167 men, 40 women) cases of primary malignancies of the nasal cavity and paranasal sinuses diagnosed between January 1986 and February 1988 at 27 hospitals in France | 409 controls were obtained from: 1) hospital cancer patients, frequency-matched for age and sex 2) controls selected from lists provided by cases matching for sex, age (± 10 yr), and residence | Physician interview to collect detailed occupational history | Shoe and leather workers: Ever employed<br>< 15 yr<br>> 15 yr<br>15 yr induction<br>Leather dust: Medium-high level | 3<br><br><br><br><br>3 | Squamous cell carcinomas: 2.1 (0.5–8.3) 1.9 (0.2–18.3) 2.3 (0.4–12.3) 2.1 (0.5–8.3) 3.1 (0.8–12.4) Adenocarcinomas: 0 cases identified | Matched on age and sex | |

## Table 2.3 (continued)

| Reference, study location and period | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | No. of cases/ deaths | OR (95%CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Battista *et al.* (1995)<br>Population-based<br>Italy | Nasal cavity and paranasal sinus (160) | 96 cases of malignant neoplasms of the nose and paranasal sinuses diagnosed during 1982–87 in the catchment areas of the hospitals of Verona, Vicenza and Siena | 378 hospital controls matched for sex, age (± 5 yr), residence and time of admission; all diagnoses were accepted except chronic rhinosinusal disease, acute nasal bleeding | Interviews or mailed questionnaires to collect work history with specific questions in particular industries | Association with occupation:<br>Leather workers<br>Shoe makers | <br><br>2 | <br>6.8 (1.9–25)<br>8.3 (1.9–36) | Matched on age, sex, and residence. 90% confidence limits used | |
| Teschke *et al.* (1997)<br>Population-based<br>Canada | Nasal cavity and paranasal sinus (160) | All incident cases with histologically confirmed primary malignant tumours age ≥ 19 yr, 1990–92 | Controls were selected randomly from 5-yr age and sex strata of the provincial voters list; frequency-matched for age and sex | Occupational histories were obtained by interview | Shoe and leather workers | | 0/48 cases and 6/159 controls | Adjusted for age, sex, and smoking | |
| L'Abbate *et al.* (1999a)<br>Pooled analysis<br>Italy, France, Netherlands, Germany, Sweden | Nasal cavity and paranasal sinus (160)<br>Adenocarcinomas and squamous cell carcinomas | 555 cases (451 men, 104 women) | 1705 controls (1464 men, 241 women) from the same studies. The control:case ratio ranged from 1 to 12.3, with an overall ratio of 3.1 | Interviews were conducted to collect lifetime occupational histories. Exposures assessed with a job–exposure matrix | Exposure to leather dust:<br>Women<br>Men<br>Adenocarcinomas<br>Squamous cell carcinomas | <br>7<br>26<br>15<br>10 | <br>2.7 (0.8–9.4)<br>1.9 (1.1–3.4)<br>3.0 (1.3–6.7)<br>1.5 (0.7–3.0) | Adjusted for age, study, sex (when applicable), smoking (when applicable) | The attributable risk for sinonasal cancer in relation to occupation was 33%.<br>Data from Hardell *et al.* (1982), Hayes *et al.* (1986), Merler *et al.* (1986), Bolm-Audorff *et al.* (1989), Comba *et al.* (1992a, b), Luce *et al.* (1992), and Magnani *et al.* (1993) |

CI, confidence interval; OR, odds ratio; RR, relative risk; SES, socioeconomic status; yr, year or years

**Table 2.4 Case–control studies on respiratory cancer in shoe workers or workers exposed to leather dust**

| Reference, study location and period | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | No. of cases | OR (95%CI) | Adjustment for potential confounders |
|---|---|---|---|---|---|---|---|---|
| Gustavsson *et al.* (1990)<br>Community-based<br>Sweden<br>1988–91 | Oral cavity (143–145), pharynx (146–149), larynx (161), oesophagus (150) | 545 incident cases (all male) of squamous cell carcinomas taken from the entire population of Swedish men aged 40–79 living in Stockholm or the southern region of Sweden | 641 controls (all male) frequency-matched to cases for age and region | Interviewed by nurses on smoking history, use of oral snuff, alcohol habits and occupational history | Leather dust:<br>All sites<br>Oral cavity<br>Pharynx<br>Larynx<br>Oesophagus | 16<br>3<br>5<br>5<br>3 | 2.1 (0.9–4.9)<br>2.2 (0.5–8.7)<br>2.8 (0.8–10.2)<br>2.1 (0.7–6.6)<br>2.6 (0.6–10.7) | Matched on age and region.<br>Adjusted for alcohol and smoking |
| Laforest *et al.* (2000)<br>Population-based France<br>1989–91 | Larynx (161) and hypopharynx (148) (squamous cell only) | 497 incident (all male) histologically confirmed cases from 15 French hospitals | 296 cancer controls from the same medical environment as cases were matched for age and recruited during 1987–91 in the same or nearby hospitals | Occupational physician interview to collect data on lifetime occupational history. Exposures assessed with a job–exposure matrix | Exposure to leather dust:<br>Never exposed<br>Ever exposed<br><br>Never exposed<br>Ever exposed | <br>288<br>8<br><br>198<br>3 | Larynx<br>1.0<br>0.9 (0.6–1.3)<br>Hypopharynx<br>1.0<br>0.8 (0.2–4.1) | Adjusted for age, smoking and alcohol consumption |
| Ruder *et al.* (2009)<br>Pooled analysis<br>Germany<br>1988–93,<br>1990–96 | Lung (162) | 4184 (3498 men, 868 women) identified during 1988–93 in Bremen, Frankfurt, and during 1990–96 in North Rhine-Westphalia, Rhineland-Palatinate, East Bavaria, the Saarland, Thuringia, and Saxony | 4253 (3541 men, 712 women) population controls matched for sex, age, and region of residence | Interviewed to collect information on job history and occupational exposure | Shoe workers:<br>Men–<br>Ever employed<br>Exposed<br>> 0–3 yr<br>> 3–30 yr<br>> 30 yr<br>Women–<br>Ever employed<br>Exposed<br>> 0–3 yr<br>> 3–30 yr<br>> 30 yr | <br>63<br><br>18<br>33<br>12<br><br>13<br><br>7<br>6<br>0 | <br>1.6 (1.0–2.5)<br><br>0.7 (0.3–1.4)<br>2.5 (1.2–5.1)<br>2.8 (0.9–9.2)<br><br>2.7 (0.8–8.8)<br><br>3.6 (0.4–32.1)<br>3.0 (0.6–14.5)<br>no data | Adjusted for smoking and asbestos exposure |

**Table 2.4 (continued)**

| Reference, study location and period | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | No. of cases | OR (95%CI) | Adjustment for potential confounders |
|---|---|---|---|---|---|---|---|---|
| Matos *et al.* (2000)<br>Hospital-based<br>Argentina<br>1994–96 | Lung (162) | 199 male patients residents in the city or in the province of Buenos Aires and admitted for treatment in any of four hospitals | 393 controls; two male control subjects hospitalized for conditions unrelated to tobacco use during the same period and residents in the same area, matched by hospital and age (± 5 yr) | Occupational history obtained by interview; occupational exposure assessed by job–exposure matrix | Occupation: leather shoes & repair<br>Industry: leather shoes & repair | 8<br>12 | 1.5 (0.5–4.2)<br>2.2 (0.8–5.8) | Adjusted for age group, hospital, pack–year and industries with $P < 0.05$ |
| Boffetta *et al.* (2003)<br>Pooled analysis France Italy, Spain, Switzerland<br>1980–83 | Larynx (161) and hypopharynx (148) | 1010 male cases with histologically confirmed epidermoid carcinomas from Turin, Varese, Pamplona, Calvados, Zaragoza, and Geneva | 2176 population-based controls from the same centres, chosen census lists, electoral roles, or population registries | Occupational histories collected by interview | Larynx/ hypopharynx<br>Shoe makers/ repair<br>Shoe finishers<br>Larynx Only<br>Shoe finishers<br>1–10 yr<br>11–20 yr<br>21+ yr | <br>15<br>7<br><br><br>3<br>4<br>0 | <br>1.2 (0.6–2.6)<br>3.2 (0.8–13.9)<br>4.4 (1.0–18.8)<br><br>4.6<br>2.7<br>0.0 | Adjusted for age, centre, alcohol, and smoking |

CI, confidence interval; OR, odds ratio; yr, year or years

**Table 2.5 Case–control studies on cancer of the bladder in shoe workers or workers exposed to leather dust**

| Reference, study location and period | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | No. of cases | OR (95%CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Cole *et al.* (1972)<br>Population-based<br>Massachusetts, USA | Bladder and lower urinary tract | 461 histologically confirmed cases of transitional or squamous cell carcinoma | 485 controls selected from the same sex and age from residents lists for the area | Lifetime work history collected by interview | Men: leather products | 79 | 2.0 (1.4–2.9) | Age and smoking | |
| | | | | | Finishing & associated | 44 | 2.7 (1.6–4.5) | | |
| | | | | | Contact with finished | 13 | 1.7 (0.9–3.4) | | |
| Silverman *et al.* (1983)<br>Population-based<br>Detroit, USA<br>1977–78 | Bladder and lower urinary tract | 303 male, histologically confirmed transitional or squamous cell carcinoma cases identified by 60/61 hospitals in the region | 296 controls selected through random-digit dialling or random selection from Health Care Finance Administration lists selected to be similar in age to cases | Lifetime work history collected by interview | Leather & leather products manufacture & repair | 4 | 0.5 (0.1–1.6) | Unadjusted | |
| | | | | | Shoe repairman and bootblack | 3 | 0.7 (0.2–3.3) | | |
| Schoenberg *et al.* (1984)<br>Population-based<br>New Jersey, USA<br>1978–79 | Bladder (188) | 658 male, histologically confirmed carcinoma cases | 1258 controls selected through random-digit dialling or random selection from Health Care Finance Administration lists selected to be similar in age to cases | Lifetime work history collected by interview | Leather worker | 19 | 1.8 (0.9–3.5) | Age and smoking | |
| | | | | | Leather products | 6 | 1.2 (0.4–3.6) | | |
| | | | | | Shoe repair/ bootblack | 9 | 1.9 (0.7–5.1) | | |
| | | | | | Leather materials | 34 | 1.9 (1.1–3.2) | | |

**Table 2.5 (continued)**

| Reference, study location and period | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | No. of cases | OR (95%CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Marrett *et al.* (1986)<br>Population-based<br>10 areas, USA<br>1978–79 | Bladder | 2982 histologically confirmed carcinoma cases | 5782 controls selected through random-digit dialling or random selection from Health Care Finance Administration lists selected to be similar in age to cases | Lifetime work history collected by interview | Leather dust<br>< 5 yr<br>5–14 yr<br>15+ yr | 42<br>21<br>6<br>13 | 1.4 (0.9–2.1)<br>1.6 (0.9–2.8)<br>0.8 (0.3–1.9)<br>1.4 (0.7–3.0) | Unadjusted | |
| Silverman *et al.* (1989)<br>Population-based<br>10 areas, USA<br>1977–78 | Bladder | 2100 histologically confirmed white male carcinoma cases. 75% of cases were interviewed. | 3874 white male controls selected through random-digit dialling (84% interviewed) or random selection from Health Care Finance Administration lists (83% interviewed) selected to be similar in age to cases | Lifetime work history collected by interview | Leather-processing workers | 13 | 1.2 (0.6–2.7) | Smoking | Further adjustment for age, area, education and other factors had no effect |
| Schumacher *et al.* (1989)<br>Population-based<br>Utah, USA<br>1977–83 | Bladder (188) | 417 (332 men and 85 women) cases identified by the Utah cancer registry | 877 (685 men and 192 women) controls selected by random-digit dialling or randomly from Health Care Finance Administration lists, frequency-matched on sex and age | Lifetime occupational histories obtained by interview | Men: Ever Leather industry<br>< 10 yr<br>≥ 10 yr<br>> 45 yr before diagnosis<br>Men: leather dust<br>Women: leather dust | <br><br><br><br>2<br>1 | 1.4 (0.5–4.0)<br>1.4 (0.5–4.6)<br>1.2 (0.1–13.4)<br>3.0 (0.6–13.8)<br>0.8 (0.1–5.1)<br>2.3 (0.03–179) | Age, smoking, religion, education | |

**Table 2.5 (continued)**

| Reference, study location and period | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | No. of cases | OR (95%CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Siemiatycki *et al.* (1994)<br>Population-based case-control study<br>Montreal, Canada<br>1979–86 | Bladder | 484 cases among male residents of the Montreal area | 1879 cancer cases from the same large study (all sites, excluding kidney) and 533 population controls from random-digit dialling | Extensive interview review by exposure assessment team | Leather workers:<br>< 10 yr<br>≥ 10 yr<br>Shoe makers:<br>< 10 yr<br>≥ 10 yr<br>Leather dust:<br>Substantial<br>Non-substantial | <br>12<br>14<br><br>5<br>1<br><br>8<br>5 | <br>1.0 (0.5–1.9)<br>0.7 (0.4–1.3)<br><br>2.0 (0.7–5.6)<br>0.3 (0.0–2.0)<br><br>0.7 (0.3–1.5)<br>0.6 (0.2–1.5) | Age, ethnicity SES, smoking, and coffee consumption | |
| Teschke *et al.* (1997)<br>Population-based<br>Canada<br>1990–92 | Bladder (188) | All incident cases ($n$ = 105) with histologically confirmed primary malignant tumours age ≥ 19 yr | Controls ($n$ = 139) selected randomly from 5-yr age and sex strata of provincial voters list; frequency-matched for age and sex | Occupational histories were obtained by interview | Shoe and leather workers | 2 | 0.4 (0.1–2.6) | Age, sex, and smoking | |
| t Mannetje *et al.* (1999b)<br>Re-analysis of 11 population-based studies<br>Germany, France, Italy, Greece, Denmark, Spain,<br>1976–96 | Bladder | 700 incident female cases, age 30–79 yr | 2425 population-based or hospital controls individually or frequency-matched on age group and geographic area | Lifetime occupational history | Shoe makers and leather goods makers | 7 | 0.4 (0.2–1.1) | Age, smoking, and study centre | |

**Table 2.5 (continued)**

| Reference, study location and period | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | No. of cases | OR (95%CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Kogevinas *et al.* (2003)<br>Re-analysis of 11 population-based studies Germany, France, Italy, Greece, Denmark, Spain, 1976–96 | Bladder | 3346 incident male cases, age 30–79 yr | 6840 population-based or hospital controls individually or frequency-matched on age group and geographic area | Lifetime occupational history | Leather workers | 48 | 1.3 (0.9–1.9) | Age, smoking, and study centre | Authors reported that risks were higher in studies conducted in 1990s vs 1980s |
| Samanic *et al.* (2008)<br>Hospital-based Spain 1998–2000 | Bladder carcinoma or in situ (1880–1889) (2337) | 1219 incident cases (1067 men, 152 women, 84% participation) from 18 hospitals, age 21–80 yr | 1465 controls (1105 men, 166 women, 88% participation) from the same hospitals with unrelated diseases and matched on sex, age, race/ethnicity, and hospital | Computer Assisted Interview (CAPI) | Leather, tanning and finishing<br>Overall<br>< 10 yr<br>≥ 10 yr | <br>28<br>10<br>18 | <br>0.8 (0.4–1.3)<br>0.9 (0.4–2.2)<br>0.7 (0.3–1.4) | Age, region, smoking, other high-risk occupation | |

CI, confidence interval; OR, odds ratio; yr, year or years; SES, socioeconomic status

## Table 2.6 Other case–control studies with results for shoe workers or workers exposed to leather dust

| Reference, study location and period | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | No. of cases | OR (95%CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Mikoczy *et al.* (1996)<br>Nested case–control study<br>Sweden<br>1900–89 | Pancreas, lung, soft tissue sarcoma | 68 cases occurred among a cohort of 2487 workers from 3 Swedish tanneries | 178 controls, 3 per case, matched on age and selected using incidence-density sampling from the same cohort | Exposure assigned by an occupational hygienist and long-term employees based on work histories | Leather dust:<br>Pancreas<br>Lung<br>Soft tissue sarcoma | <br>8<br>8<br>NR | <br>7.2 (1.4–35.9)<br>0.7 (0.2–2.1)<br>3.8 (0.3–48.0) | Age, sex, and plant | All 4 pancreas cases & 1/11 controls exposed to vegetable dust<br>No "noteworthy" associations reported for stomach, kidney, or bladder |
| Costantini *et al.* (2001)<br>Multicentre (12 areas) population-based study<br>Italy<br>1991–93 | Lymphatic and haematopoietic cancers | Incident cases age 20–74 diagnosed during 1991–93. Composed of 811 male and 639 female NHL cases, 193 male and 172 female Hodgkin disease cases, and 383 male and 269 female leukaemia cases | 1779 controls randomly selected from the general population frequency-matched on sex and age group | Interview at home to collect detailed occupational history and exposure to solvents and pesticides | Shoe makers and leather goods makers:<br>Men–<br>NHL and CLL<br>Hodgkin disease<br>All leukaemia | <br><br>30<br>3<br>7 | <br><br>1.0 (0.5–1.9)<br>1.2 (0.3–4.0)<br>0.9 (0.3–2.2) | Age | Detailed results not presented for women |

**Table 2.6 (continued)**

| Reference, study location and period | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | No. of cases | OR (95%CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Terry *et al.* (2005)<br>Population-based<br>USA & Canada<br>1986–89 | Leukaemia | 811 incident cases from a multisite study | 637 controls recruited through random-digit dialling with frequency-matching on age, sex, race, and region | Telephone interview to gather information on employment and duration in 27 occupations | Leather/shoe industry or shoe repair (1+ yr)<br>All leukaemia<br>AML | | <br>0.7 (0.3–1.5)<br>0.6 (0.3–1.5) | Age, sex, race, region, smoking, education, proxy response | Overall 84% response from cases, 34% from proxies. Overall 66% reponse rate with 13% surrogate respondents |
| Forand (2004)<br>USA<br>1981–87 | Leukaemia (204–208) | 36 incident cases during 1981–90 among men 65 yr or older, residing in the town of Union and deceased as of August 1997 | 144 controls (all men) were matched by death certificate for year of death and year of birth (± 1 yr) | Occupation and employer determined from death certificates | Employment in boot & shoe industry<br>AML<br>Leukaemia | <br>13<br>4 | <br>1.5 (0.7–3.1)<br>1.2 (0.3–4.3) | Matching on date of birth and death | |

AML, acute myeloid leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; NHL, non-hodgkin leukaemia; NR, not reported; OR, odds ratio; yr, year or years

the prevalence of leather work in the source population.]

Results of descriptive studies from the United Kingdom and the Nordic countries are presented in Table 2.1. High relative risks were observed, particularly when presenting results for adenocarcinoma (Acheson *et al.*, 1970a, 1982). Relative risks in more recent studies are somewhat lower, but still significantly elevated (Acheson *et al.*, 1982; Olsen, 1988; Andersen *et al.*, 1999).

A large excess was reported in the pooled English and Florence cohorts, based on 12 and one cases observed, respectively (Fu *et al.*, 1996). The risk of sinonasal cancer was associated with probable exposure to leather dust in the English cohort (Fu *et al.*, 1996), and the excess was reported to be greatest in the finishing area in the earlier report on the English cohort (Pippard & Acheson, 1985). Results for sinonasal cancer were not reported for the Russian and American shoe-manufacturing cohorts (Bulbulyan *et al.*, 1998; Lehman & Hein, 2006). The US cohort study reported there was 'no evidence of any significant level of exposure to leather dust.' No sinonasal cancer cases were reported in any of the three proportionate mortality ratio (PMR) studies. There were 2.2 and 1.9 expected cases in the studies of Decouflé & Walrath (1983) and Walrath *et al.* (1987), respectively. Expected numbers were not reported for Garabrant & Wegman (1984), see Table 2.2.

Fourteen sinonasal case–control studies and one pooled re-analysis of seven European studies were reviewed. Twelve of the 14 studies observed evidence of an excess of sinonasal cancer, although sometimes based on very small numbers. The largest odds ratios were observed in the Italian studies, with odds ratios in the range of 3.5 (95%CI: 0.6–2.3) (Magnani *et al.*, 1993) to 121 (95%CI: 17.3–844) for heavy leather dust exposure (Merler *et al.*, 1986). In addition, two studies reported an infinite risk (Cecchi *et al.*, 1980 with seven cases and zero controls; Bimbi *et al.*, 1988 with three cases and zero controls). Excesses were also observed in studies from Sweden (Hardell *et al.*, 1982), Japan (Shimizu *et al.*, 1989), Germany (Bolm-Audorff *et al.*, 1989, 1990), and France (Luce *et al.*, 1992, 1993). The only non-positive studies were from the USA (Brinton *et al.*, 1984) and Canada (Teschke *et al.*, 1997), the only North American studies. The pooled re-analysis of European case–control studies observed increased risks associated with leather dust exposure among both men (OR, 1.9; 95%CI: 1.1–3.4) and women (odds ratio [OR], 2.7; 95%CI: 0.8–9.4), see Table 2.3.

Relative risks (RR) for adenocarcinoma were consistently high in descriptive (Acheson *et al.*, 1970b, 1982) and case–control studies (Cecchi *et al.*, 1980; Merler *et al.*, 1986; Comba *et al.*, 1992a; 't Mannetje *et al.*, 1999a). However, smaller excess risks were also observed in the few cases where squamous cell carcinoma results were presented (Shimizu *et al.*, 1989; Luce *et al.*, 1992, 1993; 't Mannetje *et al.*, 1999a).

In reviewing trends from Northamptonshire, the United Kingdom, Acheson *et al.* (1982) noted that the majority of cases had been employed in the departments with the most dusty operations, and that they had much higher risk compared to other operatives (RR, 4.5; 95%CI: 2.8–6.8). The retrospective cohort study of workers employed in the British boot and shoe industry also observed the highest risks among workers employed in the jobs with the highest exposure to leather dust (Pippard & Acheson, 1985). This was also observed in the update of the British cohort for the pooled analysis (Fu *et al.*, 1996). An increased risk among workers with the highest leather dust exposure was also observed in case–control studies that reported results for leather dust exposure (Merler *et al.*, 1986; Luce *et al.*, 2002). Most other case–control studies did not provide details regarding leather dust exposure, although Loi *et al.* (1989) did report that four of five leather workers were milling-machine operators, a group thought to have high leather dust exposure. In a pooled analysis of European

studies 't Mannetje *et al.* (1999a) observed an excess of adenocarcinoma (OR, 3.0; 95%CI: 1.3–6.7) as well as a possible increase for squamous cell carcinoma (OR, 1.5; 95%CI: 0.7–3.0).

## 2.2 Other respiratory cancers

None of the cohort or PMR studies reported results for the pharynx alone (Table 2.2). Among the three US PMR studies, Decouflé & Walrath (1983) and Walrath *et al.* (1987) observed slightly more cases than expected, but Garabrant & Wegman (1984) observed slightly less cases than expected. Tarvainen *et al.* (2008) observed an excess of oral and pharyngeal cancer among shoe makers in Finland based on only two cases. Gustavsson *et al.* (1998) observed an excess risk of squamous cell cancer associated with leather dust for both oral (OR, 2.2; 95%CI: 0.5–8.7) and pharyngeal (OR, 2.8; 95%CI: 0.8–10.2) cancer. Laforest *et al.* (2000) found no association between exposure to leather dust and squamous cell carcinoma of the hypopharynx. Boffetta *et al.* (2003) did not report separate results for the pharynx, but observed an excess of carcinomas of the larynx and hypopharynx among shoe finishers, but not shoe makers or repairers, see Table 2.4.

No excesses of cancer of the larynx were observed in the updated English or Italian cohorts or the three PMR studies (Table 2.2). Results for cancer of the larynx were not reported in the Russian or US cohorts. Gustavsson *et al.* (1998) observed an excess risk of squamous cell carcinoma of the larynx associated with leather dust exposure (OR, 2.1; 95%CI: 0.7–6.6). Laforest *et al.* (2000) found no association (OR, 0.9; 95%CI: 0.6–1.3) between exposure to leather dust and squamous cell carcinoma of the larynx. Boffetta *et al.* (2003) observed an excess of carcinoma of the larynx among shoe finishers (OR, 4.4; 95%CI: 1.0–18.8) that was not associated with duration of employment.

No excesses of lung cancer were observed in the updated English or Italian cohorts (Fu *et al.*, 1996). An excess was observed among men, but not among women in the Russian cohort (Bulbulyan *et al.*, 1998). The excess was limited to workers exposed to non-solvents who were also identified as having potential exposure to leather dust. An excess of lung cancer among both men and women was observed in the US cohort, which was not related to duration of employment (Lehman & Hein, 2006). Using indirect methods, the authors estimated that part, but not all, of the excess could be due to increased smoking rates among blue-collar workers. Although a small, but significant excess of lung cancer was observed among men (PMR, 1.2; $P < 0.05$) in Decouflé & Walrath (1983), no such excess was observed among women in the same study or among either sex in the other two PMR studies. In a pooled analysis of two German case–control studies, an excess risk for lung cancer among both male and female shoe workers was observed (Jöckel *et al.*, 2000). An excess was also observed in a a small Argentine case–control study (Matos *et al.*, 2000).

## 2.3 Leukaemia

Early studies reported in the previous *IARC Monograph* identified an unusually high prevalence of leukaemia and aplastic anaemia among shoe workers exposed to benzene in both Italy and Turkey (Aksoy *et al.*, 1974, 1976; Vigliani, 1976; Vigliani & Forni, 1976; Aksoy & Erdem, 1978). An excess was also identified in the Italian cohort study where benzene exposures were reported to be very high until 1963 when regulations were changed (Paci *et al.*, 1989; Fu *et al.*, 1996). An excess of leukaemia was observed among workers in the Russian cohort compared to the general population, and all five were in the highest solvent-exposed group (Bulbulyan *et al.*, 1998). All five of these cases were employed before 1960 when co-exposure to benzene was possible.

No excess was observed in the updated English cohort (Fu *et al.*, 1996). No excess of leukaemia was observed in the US cohort study (Lehman & Hein 2006). However, benzene was not detected in industrial hygiene surveys for the US study and "company management asserted that benzene had never been present in the solvents used at either of the plants." No excesses were observed in the three US PMR studies. Andersen *et al.* (1999) also did not observe an excess in the Nordic Census to tumour registry linkage study. More recent case–control studies, including a large, multicentre Italian study with cases diagnosed during 1991–93, have not observed an excess risk for leukaemia associated with employment in the leather industries (Costantini *et al.*, 2001; Forand, 2004; Terry *et al.*, 2005).

## 2.4 Cancer of the bladder

An excess of cancer of the bladder was not observed in the updated British, Italian, or US cohorts (Fu *et al.*, 1996; Lehman & Hein, 2006). A significant excess of cancer of the bladder was observed among women shoe workers (PMR, 2; $P < 0.05$) in Decouflé & Walrath (1983). However, no excess was observed among men. No excess of cancer of the bladder among either sex in another PMR study was found (Walrath *et al.*, 1987). Pukkala *et al.* (2009) observed a slight excess in the Nordic Census to tumour registry linkage study (SIR, 1.08; 95%CI: 0.98–1.19).

Results for cancer of the bladder from 11 case–control studies are presented in Table 2.5. Two studies, both using broad definitions of leather work, observed strong evidence of an excess risk. Cole *et al.* (1972) observed an excess risk among leather-product workers. Schoenberg *et al.* (1984) observed an excess among men working with leather materials. Several studies observed very small excesses associated with leather work. Marrett *et al.* (1986) found a very weak association associated with leather dust. Schumacher *et al.* (1989) found very weak evidence of an excess risk associated with the leather industry, but not with leather dust. Kogevinas *et al.* (2003) observed a possible small excess among men from 11 European studies in a pooled re-analysis but 't Mannetje *et al.* (1999b) observed a decreased risk among women from the same studies. Other studies either observed no risk or a decreased risk for cancer of the bladder among leather workers. Silverman *et al.* (1983) did not observe an excess among either leather products workers or shoe repairers in Detroit, USA. Silverman *et al.* (1989) did not observe an excess among either leather processing workers from ten regions of the USA. Siemiatycki *et al.* (1994) and Teschke *et al.* (1997) found no evidence of an association with leather or shoe work. Samanic *et al.* (2008) also did not observe an excess for cancer of the bladder associated with leather industry workers in Spain. [The Working Group noted that the results of Silverman *et al.* (1983) and Marrett *et al.* (1986) were not adjusted for smoking.]

## 2.5 Other cancers

Excesses of other cancers have been observed in some studies, but no consistent pattern has emerged (Decouflé & Walrath, 1983; Garabrant & Wegman, 1984; Walrath *et al.*, 1987; Mikoczy *et al.*, 1996; Bulbulyan *et al.*, 1998).

## 2.6 Synthesis

There is consistent and strong evidence from both descriptive and case–control studies associating work in the boot and shoe industry with an increased risk of cancer of the nasal cavity and paranasal sinuses. Among those studies with histological classification of the tumours, very large excess risks were observed for sinonasal adenocarcinoma. When examined in case–control studies, the Brittish cohort study, and case series, this excess appears among workers with the highest leather dust exposure. There

is strong evidence that exposure to leather dust causes cancer of the nasal cavity and paranasal sinuses.

Clusters of leukaemia cases were reported among workers with benzene exposure in the shoe industries of Italy and Turkey in the 1970s. An excess was also observed in an Italian cohort study and among a subgroup of a Russian cohort where benzene exposure was likely to have occurred. A case–control study in Italy did not observe an excess in the industry after changes in industrial practices resulted in large reductions in benzene exposure. Benzene is already recognized as a cause of leukaemia, and is likely to be the explaination of the previous excess observed in the industry.

Several early studies reported an excess risk of bladder cancer among leather workers. Two case–control studies observed an association with the leather industry, but many more recent studies found little or no association with the leather industry when tanning was not considered. For other cancer sites, no consistent pattern of excess risk was observed or too little data was available to adequately assess causality with boot and shoe manufacturing.

## 3. Cancer in Experimental Animals

No data were available to the Working Group.

## 4. Other Relevant Data

See Section 4 of the *Monograph* on Wood Dust in this Volume.

## 5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of leather dust. Leather dust causes cancer of the nasal cavity and paranasal sinuses.

No data in experimental animals for the carcinogenicity of leather dust were available to the Working Group.

Leather dust is *carcinogenic to humans (Group 1).*

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# SILICA DUST, CRYSTALLINE, IN THE FORM OF QUARTZ OR CRISTOBALITE

Silica was considered by previous IARC Working Groups in 1986, 1987, and 1996 (IARC, 1987a, b, 1997). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

## 1. Exposure Data

Silica, or silicon dioxide ($SiO_2$), is a group IV metal oxide, which naturally occurs in both crystalline and amorphous forms (i.e. polymorphic; NTP, 2005). The various forms of crystalline silica are: α-quartz, β-quartz, α-tridymite, β-tridymite, α-cristobalite, β-cristobalite, keatite, coesite, stishovite, and moganite (NIOSH, 2002). The most abundant form of silica is α-quartz, and the term quartz is often used in place of the general term crystalline silica (NIOSH, 2002).

### 1.1 Identification of the agent

α-Quartz is the thermodynamically stable form of crystalline silica in ambient conditions. The overwhelming majority of natural crystalline silica exists as α-quartz. The other forms exist in a metastable state. The nomenclature used is that of α for a lower-temperature phase, and β for a higher-temperature phase. Other notations exist and the prefixes low- and high- are also used (IARC, 1997). The classification and nomenclature of silica forms are summarized in Table 1.1. For more detailed information, refer to the previous *IARC Monograph* (IARC, 1997).

### 1.2 Chemical and physical properties of the agent

Selected chemical and physical properties of silica and certain crystalline polymorphs are summarized in Table 1.1. For a detailed discussion of the crystalline structure and morphology of silica particulates, and corresponding physical properties and domains of thermodynamic stability, refer to the previous *IARC Monograph* (IARC, 1997).

### 1.3 Use of the agent

The physical and chemical properties of silica make it suitable for many uses. Most silica in commercial use is obtained from naturally occurring sources, and is categorized by end-use or industry (IARC, 1997; NTP, 2005). The three predominant commercial silica product categories are: sand and gravel, quartz crystals, and diatomites.

**Table 1.1 Nomenclature, CAS numbers, and classification of silica forms with selected physical and chemical properties**

| Name | CAS No. | Basic Formula | Classification | Synonyms | Properties |
|---|---|---|---|---|---|
| Silica | 7631-86-9 | $SiO_2$ | α-quartz, β-quartz; α-tridymite, β1-tridymite, β2-tridymite; α-cristobalite, β-cristobalite; coesite; stishovite; moganite | | Structure: crystalline, amorphous, cryptocrystalline<br>Molecular weight: 60.1<br>Solubility: poorly soluble in water at 20 °C and most acids; increases with temperature and pH<br>Reactivity: reacts with alkaline aqueous solutions, with hydrofluoric acid (to produce silicon tetrafluoride gas), and catechol |
| **Crystalline Silica** | | | | | |
| Cristobalite | 14464-46-1 | | α-cristobalite, β-cristobalite | | |
| Quartz | 14808-60-7 | | α-quartz, β-quartz | α-quartz: agate; chalcedony; chert; flint; jasper; novaculite; quartzite; sandstone; silica sand; tripoli | Solubility: 6–11 µg/cm$^3$ (6–11 ppm) at room temperature; slightly soluble in body fluids<br>Thermodynamic properties: melts to a glass; coefficient of expansion by heat—lowest of any known substance |
| Tripoli | 1317-95-9 | | | | |
| Tridymite | 15468-32-3 | | α-tridymite, β1-tridymite, β2-tridymite | | |

From IARC (1997), NIOSH (2002), NTP (2005)

### *1.3.1 Sand and gravel*

Although silica sand has been used for many different purposes throughout history, its most ancient and principal use has been in the manufacture of glass (e.g. containers, flat plate and window, and fibreglass). Sands are used in ceramics (e.g. pottery, brick, and tile), foundry (e.g. moulding and core, refractory), abrasive (e.g. blasting, scouring cleansers, sawing and sanding), hydraulic fracturing applications, and many other uses. Several uses require the material to be ground (e.g. scouring cleansers, some types of fibreglass, certain foundry applications). In some uses (e.g. sandblasting, abrasives), grinding also occurs during use. For a more complete list of end-uses, refer to Table 8 of the previous *IARC Monograph* (IARC, 1997).

According to the US Geological Survey, world production in 2008 was estimated to be 121 million metric tons (Dolley, 2009). The leading producers were the USA (30.4 million metric tons), Italy (13.8 million metric tons), Germany (8.2 million metric tons), the United Kingdom (5.6 million metric tons), Australia (5.3 million metric tons), France (5 million metric tons), Spain (5 million metric tons), and Japan (4.5 million metric tons).

### 1.3.2 Quartz crystals

Quartz has been used for several thousand years in jewellery as a gem stone (e.g. amethyst, citrine), and is used extensively in both the electronics and optical components industries. Electronic-grade quartz is used in electronic circuits, and optical-grade quartz is used in windows, and other specialized devices (e.g. lasers) (IARC, 1997).

### 1.3.3 Diatomites

Diatomites are used in filtration, as fillers (in paint, paper, synthetic rubber goods, laboratory absorbents, anti-caking agents, and scouring powders), and as carriers for pesticides. They impart abrasiveness to polishes, flow and colour qualities to paints, and reinforcement to paper. Other uses include: insulators, absorption agents, scourer in polishes and cleaners, catalyst supports, and packing material (IARC, 1997).

According to the US Geological Survey, world production in 2008 was estimated to be 2.2 million metric tons. The USA accounted for 35% of total world production, followed by the People's Republic of China (20%), Denmark (11%), Japan (5%), Mexico (4%), and France (3%) (Crangle, 2009).

## 1.4 Environmental occurrence

Keatite, coesite, stishovite, and moganite are rarely found in nature. The most commonly occurring polymorphs are quartz, cristobalite and tridymite, which are found in rocks and soil. These forms of silica can be released to the environment via both natural and anthropogenic sources (e.g. foundry processes, brick and ceramics manufacturing, silicon carbide production, burning of agricultural waste or products, or calcining of diatomaceous earth). Some of these anthropogenic activities may cause transformation of one polymorph into another (NIOSH, 2002).

### 1.4.1 Natural occurrence

α-Quartz is found in trace to major amounts in most rock types (e.g. igneous, sedimentary, metamorphic, argillaceous), sands, and soils. The average quartz composition of major igneous and sedimentary rocks is summarized in Table 10 of the previous *IARC Monograph* (IARC, 1997). Quartz is a major component of soils, composing 90–95% of all sand and silt fractions in a soil. It is the primary matrix mineral in the metalliferous veins of ore deposits, and can also be found in semiprecious stones, such as amethyst, citrine, smoky quartz, morion, and tiger's eye (IARC, 1997).

Crystalline tridymite and cristobalite are found in acid volcanic rocks. Cristobalite also occurs in some bentonite clays, and as traces in diatomite. Although rarely found in nature, coesite and stishovite have been found in rocks that equilibrated in short-lived high-pressure environments (e.g. meteoritic impact craters), and keatite has been found in high-altitude atmospheric dusts, which are believed to originate from volcanic sources (IARC, 1997).

For a more detailed description of the natural occurrence of crystalline silica and its polymorphs in air, water and soil, refer to the previous *IARC Monograph* (IARC, 1997).

## 1.5 Human exposure

### 1.5.1 Exposure of the general population

Inhalation of crystalline silica during the use of commercial products containing quartz is thought to be the primary route of exposure for the non-occupationally exposed (i.e. general) population. Commercial products containing quartz include: cleansers, cosmetics, art clays and glazes, pet litter, talcum powder, caulk, putty, paint, and mortar. No quantitative data on potential levels of exposurem during the use of these products were available at the time of

writing (WHO, 2000). The general population may also be exposed via ingestion of potable water containing quartz particles; however, quantitative data on concentrations of quartz in potable or other forms of drinking-water were again not available (IARC, 1997; WHO, 2000).

### 1.5.2 Occupational exposure

Because of the extensive natural occurrence of crystalline silica in the earth's crust and the wide uses of the materials in which it is a constituent, workers may be exposed to crystalline silica in a large variety of industries and occupations (IARC, 1997). Table 1.2 lists the main industries and activities in which workers could be exposed to crystalline silica. Included in this table are activities that involve the movement of earth (e.g. mining, farming, construction, quarrying), disturbance of silica-containing products (e.g. demolition of masonry and concrete), handling or use of sand- and other silica-containing products (e.g. foundry processes, such as casting, furnace installation and repair; abrasive blasting; production of glass, ceramics, abrasives, cement, etc.).

Estimates of the number of workers potentially exposed to respirable crystalline silica have been developed by the National Institute of Occupational Safety and Health (NIOSH) in the USA and by CAREX (CARcinogen EXposure) in Europe. Based on the National Occupational Exposure Survey (NOES), conducted during 1981–83, and the *County Business Patterns 1986*, NIOSH estimated that about 1.7 million US workers were potentially exposed to respirable crystalline silica (NIOSH, 2002). Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX database estimates that more than 3.2 million workers in the then 15 Member States of the European Union during 1990–93 were considered as occupationally exposed to respirable crystalline silica above background level (Kauppinen *et al.*, 2000). Nearly 87% of these workers were employed in 'construction' ($n$ = 2080000), 'manufacture of other non-metallic mineral products' ($n$ = 191000), 'other mining' ($n$ = 132000), 'manufacture of pottery, china and earthenware' ($n$ = 96000), 'manufacture of machinery except electrical' ($n$ = 78000), 'iron and steel basic industries' ($n$ = 68000), 'manufacture of fabricated metal products, except machinery and equipment' ($n$ = 68000), and 'metal ore mining' ($n$ = 55000). The countries with the highest number of potentially exposed workers were: Germany (1 million workers), the United Kingdom (580000 workers), Spain (400000 workers), Italy (250000 workers), the Netherlands (170000 workers), France (110000 workers), and Austria (100000 workers) (Kauppinen *et al.*, 2000; Mirabelli & Kauppinen, 2005; Scarselli *et al.*, 2008).

For representative data in the main industries where quantitative exposure levels were available in the published literature and/or where major occupational health studies had been conducted, refer to the previous *IARC Monograph* (IARC, 1997). These main industries include mines and quarries, foundries and other metallurgical operations, ceramics and related industries, construction, granite, crushed stone and related industries, sandblasting of metal surfaces, agriculture, and miscellaneous other operations (IARC, 1997). Data from studies and reviews on crystalline silica exposure published since the previous *IARC Monograph* are summarized below.

#### (a) Levels of occupational exposure

To estimate the number of US workers potentially exposed to high levels of crystalline silica and to examine trends in exposure over time, Yassin *et al.* (2005) analysed data contained in the OSHA Integrated Management Information System (IMIS) database. After exclusion of duplicate bulk and area samples, a total of 7209 personal sample measurements collected during

**Table 1.2 Main activities in which workers may be exposed to crystalline silica**

| Industry/activity | Specific operation/task | Source material |
|---|---|---|
| Agriculture | Ploughing, harvesting, use of machinery | Soil |
| Mining and related milling operations | Most occupations (underground, surface, mill) and mines (metal and non-metal, coal) | Ores and associated rock |
| Quarrying and related milling operations | Crushing stone, sand and gravel processing, monumental stone cutting and abrasive blasting, slate work, diatomite calcination | Sandstone, granite, flint, sand, gravel, slate, diatomaceous earth |
| Construction | Abrasive blasting of structures, buildings<br>Highway and tunnel construction<br>Excavation and earth-moving<br>Masonry, concrete work, demolition | Sand, concrete<br>Rock<br>Soil and rock<br>Concrete, mortar, plaster |
| Glass, including fibreglass | Raw material processing<br>Refractory installation and repair | Sand, crushed quartz<br>Refractory materials |
| Cement | Raw materials processing | Clay, sand, limestone, diatomaceous earth |
| Abrasives | Silicon carbide production<br>Abrasive products fabrication | Sand<br>Tripoli, sandstone |
| Ceramics, including bricks, tiles, sanitary ware, porcelain, pottery, refractories, vitreous enamels | Mixing, moulding, glaze or enamel spraying, finishing | Clay, shale, flint, sand, quartzite, diatomaceous earth |
| Iron and steel mills | Refractory preparation and furnace repair | Refractory material |
| Silicon and ferro-silicon | Raw materials handling | Sand |
| Foundries (ferrous and non-ferrous) | Casting, shaking out<br>Abrasive blasting, fettling<br>Furnace installation and repair | Sand<br>Sand<br>Refractory material |
| Metal products including structural metal, machinery, transportation equipment | Abrasive blasting | Sand |
| Shipbuilding and repair | Abrasive blasting | Sand |
| Rubber and plastics | Raw material handling | Fillers (tripoli, diatomaceous earth) |
| Paint | Raw materials handling | Fillers (tripoli, diatomaceous earth, silica flour) |
| Soaps and cosmetics | Abrasive soaps, scouring powders | Silica flour |
| Asphalt and roofing felt | Filling and granule application | Sand and aggregate, diatomaceous earth |
| Agricultural chemicals | Raw material crushing, handling | Phosphate ores and rock |
| Jewellery | Cutting, grinding, polishing, buffing | Semiprecious gems or stones, abrasives |
| Dental material | Sandblasting, polishing | Sand, abrasives |
| Automobile repair | Abrasive blasting | Sand |
| Boiler scaling | Coal-fired boilers | Ash and concretions |

From IARC, 1997

2512 OSHA inspections during 1988–2003 were analysed. The findings suggest that geometric mean crystalline silica exposure levels declined in some high-risk construction industries during the period under study, and revealed a significant decline when compared with silica exposure levels found in a previous study by Stewart & Rice (1990). Geometric mean airborne silica exposure levels among workers in the following industries were significantly lower in 1988–2003

than in 1979–87: general contractor industry (0.057 mg/m$^3$ versus 0.354 mg/m$^3$), bridge-tunnel construction industry (0.069 mg/m$^3$ versus 0.383 mg/m$^3$), and stonework masonry industry (0.065 mg/m$^3$ versus 0.619 mg/m$^3$). Silica exposures in the grey-iron industry also declined by up to 54% for some occupations (e.g. the geometric mean for "furnace operators" in 1979–87 was 0.142 mg/m$^3$ versus 0.066 mg/m$^3$ in 1988–2003). [The Working Group noted that exposure levels may not have decreased globally.]

Table 1.3 presents the more recent studies that assessed the levels of respirable crystalline silica in a range of industries and countries. Other recent exposure studies that did not measure the respirable crystalline silica components are presented below.

### (b) Mines

As part of a cohort mortality study follow-up in four tin mines in China, Chen *et al.* (2006) developed quantitative exposure estimates of silica mixed dust. Workers in the original cohort were followed up from the beginning of 1972 to the end of 1994. Cumulative exposure estimates were calculated for each worker using their mine employment records and industrial hygiene measurements of airborne total dust, particle size, and free silica content collected since the 1950s. Total dust concentrations of the main job titles exposed were found to have declined from about 10–25 mg/m$^3$ in the beginning of the 1950s to about 1–4 mg/m$^3$ in the 1980s and 1990s. The respirable fraction of total dust was estimated to be 25 ± 4%, and the respirable crystalline silica concentration was estimated to be 4.3% of the total mixed mine dust

Tse *et al.* (2007) conducted a cross-sectional study to investigate the prevalence of accelerated silicosis among 574 gold miners in Jiangxi, China. Using occupational hygiene data abstracted from government documents and bulk dust data from a study in another gold mine in the region, the estimated mean concentration of respirable silica dust were reported as 89.5 mg/m$^3$ (range, 70.2–108.8 mg/m$^3$). According to government documents, the total dust concentration in underground gold mining was in the range of 102.6–159 mg/m$^3$ (average, 130.8 mg/m$^3$), and the fraction of silica in total dust was around 75.7–76.1%. No data on the proportion of respirable dust were available.

To determine dose–response relationships between exposure to respirable dust and respiratory health outcomes, Naidoo *et al.* (2006) used historical data ($n$ = 3645) and current measurements ($n$ = 441) to characterize exposure to respirable coal mine dust in three South African coal mines. Jobs were classified into the following exposure zones: face (directly involved with coal extraction), underground backbye (away from the coal mining face), and work on the surface. Based on the 8-hour full-shift samples collected respectively, mean respirable dust concentrations in Mines 1, 2, and 3, were as follows: 0.91 mg/m$^3$ (GSD, 3.39; mean silica content, 2.3%; $n$ = 102), 1.28 mg/m$^3$ (GSD, 2.11; mean silica content, 1.4%; $n$ = 63), and 1.90 mg/m$^3$ (GSD, 2.23; mean silica content, 2.7%; $n$ = 73) at the face; 0.48 mg/m$^3$ (GSD, 2.97; mean silica content, 1.48%; $n$ = 30), 0.56 mg/m$^3$ (GSD, 3.71; mean silica content, 1.35%; $n$ = 47), and 0.52 mg/m$^3$ (GSD, 4.06; mean silica content, 0.9%; $n$ = 41) in the backbye zone; and, 0.31 mg/m$^3$ (GSD, 3.52; mean silica content, 0.95%; $n$ = 8), 0.15 mg/m$^3$ (GSD, 3.56; $n$ = 6), and 0.24 mg/m$^3$ (GSD, 7.69; mean silica content, 0.64%; $n$ = 11) in the surface zone. Based on the historical data, overall geometric mean dust levels were 0.9 mg/m$^3$ (GSD, 4.9), 1.3 mg/m$^3$ (GSD, 3.3), and 0.5 mg/m$^3$ (GSD, 5.6) for Mines 1, 2, and 3, respectively.

### (c) Granite-quarrying and -processing, crushed stone, and related industries

Bahrami *et al.* (2008) described the personal exposure to respirable dust and respirable quartz in stone-crushing units located in western Islamic Republic of Iran. A total of 40 personal samples

## Table 1.3 Respirable crystalline silica concentrations in various industries worldwide

| Reference, industry and country, period (if reported) | Site, occupation, or exposure circumstance | Concentration of respirable crystalline silica (mg/m³) | Number of samples | Comments |
|---|---|---|---|---|
| **Mines** | | | | |
| Hayumbu *et al.* (2008), copper mines, the Zambia | | Arithmetic mean (SD; range) | | Cross-sectional dust exposure assessment; bulk and personal respirable samples; NIOSH method 0600 for gravimetric analysis of respirable dust; NIOSH method 7500 for quartz analysis of bulk and respirable samples; mean personal sampling time: 307 minutes (Mine 1) and 312 minutes (Mine 2) |
| | Mine 1 | 0.14 (0.2; 0–1.3) | 101 | |
| | Mine 2 | 0.06 (0.06; 0–0.3) | 102 | |
| Weeks & Rose (2006), metal and non-metal mines, USA, 1998–2002 | | Arithmetic mean (GM) | | Mine Safety and Health Administration compliance data from 4726 mines; 8-hour full-shift personal air samples; gravimetric analysis of respirable dust; NIOSH method 7500 for silica analysis; arithmetic and geometric mean exposure calculated and classified by occupation, mine, and state |
| | Strip and open pit mines | 0.047 (0.027) | 13702 | |
| | Mills or preparation plants | 0.045 (0.027) | 1145 | |
| | Underground mines | 0.050 (0.029) | 1360 | |
| | Overall | 0.047 (0.027) | 16207 | |
| Brâtveit *et al.* (2003) underground small-scale mining, United Republic of Tanzania, 2001 | | Geometric mean (GSD) | | Personal dust sampling (respirable and total dust) on 3 consecutive day shifts; sampling time varied between 5 and 8 hours; gravimetric analysis of respirable and total dust; NIOSH method 7500 for silica analysis |
| | Drilling, blasting, and shovelling | 2.0 (1.7) | 6 | |
| | Shovelling and loading of sacks | 1.0 (1.5) | 3 | |
| | Overall | 1.6 (1.8) | 9 | |
| Park *et al.* (2002) diatomaceous earth mining and milling, California, USA, 1942–94 | Mines and mills | Arithmetic mean 0.29 Cumulative exposure (mg/m³–yr) 2.16 | NR | Re-analysis of data from a cohort of 2342 California diatomaceous earth workers; mean concentration of respirable crystalline silica averaged over years of employment of cohort; crystalline silica content of bulk samples varied from 1–25%, and depended on process location |
| Mamuya *et al.* (2006) underground coal mining, United Republic of Tanzania; June–August 2003 and July–August 2004 | | Geometric mean (GSD) | | Personal dust samples collected during two periods in 2003 and 2004; 134 respirable dust samples collected and analysed gravimetrically; 125 samples analysed for quartz using NIOSH method 7500 |
| | Development team | 0.073 (11.1) | 56 | |
| | Mine team | 0.013 (2.97) | 45 | |
| | Transport team | 0.006 (1.84) | 11 | |
| | Maintenance team | 0.016 (11.05) | 13 | |
| | Overall | 0.027 (8.18) | 125 | |

**Table 1.3 (continued)**

| Reference, industry and country, period (if reported) | Site, occupation, or exposure circumstance | Concentration of respirable crystalline silica (mg/m$^3$) | Number of samples | Comments |
|---|---|---|---|---|
| **Granite-quarrying and -processing, crushed stone, and related industries** | | | | |
| Wickman & Middendorf (2002)<br>Granite–quarrying, Georgia, USA; May 1993–February 1994 | Granite sheds | Arithmetic mean (SD)<br>0.052 (0.047) | 40 | Exposure assessment surveys in 10 granite sheds to measure compliance; full-shift respirable dust samples in workers' breathing zone and area samples; gravimetric analysis of respirable dust; crystalline silica analysis using OSHA ID 142; TWA exposures calculated |
| Brown & Rushton (2005a)<br>Industrial silica sand, United Kingdom, 1978–2000 | Quarries | Unadjusted geometric mean (GSD)<br>0.09 (3.9) | 2429 (personal)<br>583 (static) | Samples collected by companies as part of routine monitoring programme; gravimetric analysis; silica content measured by Fourier transform infrared spectrophotometry until 1997 and by X-ray diffraction thereafter; personal and static measurements combined into one data set |
| Gottesfeld *et al.* (2008)<br>Stone–crushing mills, India, 2003 (initial phase), 2006 and 2007 (post-implementation of engineering controls) | | Arithmetic mean (SD) | | Bulk and personal air samples collected; silica analysis using NIOSH method 7500; NIOSH method 0500 for respirable particulates used in 2003 |
| | Prior to water-spray controls (2003) | Cristobalite, 0.09 (0.08) | [5] | |
| | | Quartz, 0.25 (0.12) | [5] | |
| | After water-spray controls | | | |
| | Monsoon season (winter 2007) | Cristobalite, 0.02 (0.01) | [18] | |
| | | Quartz, 0.01 (0.01) | [18] | |
| | Dry season (summer 2006) | Cristobalite, 0.03 (0.03) | [27] | |
| | | Quartz, 0.06 (0.12( | [27] | |
| Yingratanasuk *et al.* (2002)<br>Stone carvers, Thailand, 1999–2000 | | Arithmetic mean | 148 (total number of samples) | Cross-sectional study design; full-shift (8-hour) personal dust samples; respirable dust analysed gravimetrically; silica analysis by infrared spectrophotometry |
| | Carvers (Site 1) | 0.22 | | |
| | Pestle makers (Site 1) | 0.05 | | |
| | Mortar makers (Site 2) | 0.05 | | |
| | Mortar makers (Site 3) | 0.88 | | |

**Table 1.3 (continued)**

| Reference, industry and country, period (if reported) | Site, occupation, or exposure circumstance | Concentration of respirable crystalline silica ($mg/m^3$) | Number of samples | Comments |
|---|---|---|---|---|
| Rando *et al.* (2001)<br>Industrial sand industry, North America, 1974–98 | Sand-processing plants | Geometic mean<br>0.042 (overall) | 14249 | Exposure estimates created for a longitudinal and case-referent analysis of a cohort of industrial sand workers; gravimetric analysis of total dust; silica analysis by X-ray diffraction spectroscopy |
| Yassin *et al.* (2005)<br>Stonework masonry, USA, 1988–2003 | All occupations | Geometric mean (GSD)<br>0.065 (0.732) | 274 | Analysis of personal silica measurements ($n$ = 7209) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections |
| **Foundries** | | | | |
| Andersson *et al.* (2009)<br>Iron foundry, Sweden, April 2005–May 2006 | | Geometric mean (GSD) | | Respirable dust, quartz, cristobalite, trydimite samples collected on 2 consecutive workdays for shift and daytime workers; gravimetric analysis conducted using modified NIOSH method; respirable quartz and cristobalite analysed using modified NIOSH method 7500 |
| | Caster | 0.020 (1.8) | 22 | |
| | Core Maker | 0.016 (2.3) | 55 | |
| | Fettler | 0.041 (2.9) | 115 | |
| | Furnace and ladle repair | 0.052 (3.7) | 33 | |
| | Maintenance | 0.021 (2.6) | 26 | |
| | Melter | 0.022 (2.0) | 49 | |
| | Moulder | 0.029 (2.6) | 64 | |
| | Sand mixer | 0.020 (2.3) | 14 | |
| | Shake out | 0.060 (1.7) | 16 | |
| | Transportation | 0.017 (2.6) | 13 | |
| | Other | 0.020 (2.0) | 28 | |
| | All occupations | 0.028 (2.8) | 435 | |

**Table 1.3 (continued)**

| Reference, industry and country, period (if reported) | Site, occupation, or exposure circumstance | Concentration of respirable crystalline silica (mg/m$^3$) | Number of samples | Comments |
|---|---|---|---|---|
| Yassin *et al.* (2005)<br>Grey–iron foundry, USA 1988–2003 | | Geometric mean (GSD) | | Analysis of personal silica measurements ($n$ = 7 209) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections |
| | Spruer | 0.154 (0.100) | 22 | |
| | Hunter operator | 0.093 (1.144) | 10 | |
| | Charger | 0.091 (0.999) | 8 | |
| | Core maker | 0.078 (1.033) | 89 | |
| | Grinder | 0.075 (0.821) | 371 | |
| | Molder | 0.073 (0.910) | 308 | |
| | Abrasive blast operator | 0.070 (0.821) | 56 | |
| | Sorter | 0.067 (0.827) | 23 | |
| | Reline cupola | 0.067 (0.725) | 29 | |
| | Furnace operator | 0.066 (0.766) | 47 | |
| | Core setter | 0.066 (0.671) | 23 | |
| | Craneman | 0.066 (0.815) | 16 | |
| | Cleaning department | 0.060 (0.879) | 36 | |
| | Inspector | 0.057 (1.298) | 21 | |
| | Ladle repair | 0.055 (0.829) | 30 | |
| **Other metallurgical operations** | | | | |
| Forceland *et al.* (2008)<br>Silicon carbide industry, Norway, November 2002–December 2003 | | Geometric mean | 720 (total) | Exposure survey conducted in 3 silicon carbide plants; measurements collected to improve previously developed job–exposure matrix; sampling duration close to full shift (6–8 hours); 2 sampling periods of 2 work weeks; gravimetric analysis of respirable dust; silica analysis using modified NIOSH method 7500 |
| | Cleaning operators (Plant A) | 0.020 (quartz) | | |
| | Mix operators (Plants A and C), charger/ mix and charger operators (Plant C) | 0.008–0.013 (quartz) | | |
| | All other jobs (Plants A, B and C) | < 0.005 (quartz) | | |
| | Charger/mix operators (Plant C) | 0.038 (cristobalite) | | |
| **Construction** | | | | |
| Tjoe-Nij *et al.* (2003)<br>Construction, the Netherlands | | Geometric mean (GSD) | | Cross-sectional study design; repeated dust measurements ($n$ = 67) on 34 construction workers; full-shift (6–8 hours) personal respirable dust sampling; gravimetric analysis of respirable dust; silica analysis by infrared spectroscopy (NIOSH method 7602); 8-h TWA concentrations calculated |
| | Concrete drillers and grinders | 0.42 (5.0) | 14 | |
| | Tuck pointers | 0.35 (2.8) | 10 | |
| | Demolition workers | 0.14 (2.7) | 21 | |

**Table 1.3 (continued)**

| Reference, industry and country, period (if reported) | Site, occupation, or exposure circumstance | Concentration of respirable crystalline silica ($mg/m^3$) | Number of samples | Comments |
|---|---|---|---|---|
| Akbar-Khanzadeh & Brillhart (2002)<br>Construction, USA | Concrete–finishing (grinding) | Arithmetic mean (SD)<br>1.16 (1.36) | 49 | Task-specific silica exposure assessment conducted as part of an OSHA Consultation Service in Ohio; gravimetric analysis of respirable samples using NIOSH method 0600; silica analysis using in-house method based on NIOSH method 7500 and OSHA ID 142 |
| Verma *et al.* (2003) | | Range (min–max) | | Task-based exposure assessment conducted as part of an epidemiological study of Ontario construction workers; personal dust sampling and direct–reading particulate monitoring; gravimetric analysis of respirable dust using modified NIOSH method 0600; respirable silica analysis using modified NIOSH method 7500 |
| | Labourers | 0.10–0.15 | 20 | |
| | Operating engineers | 0.04–0.06 | 3 | |
| | Carpenters, iron workers, masons, painters, terrazzo workers | below detectable limits | 17 | |
| Woskie *et al.* (2002)<br>Heavy and highway construction, USA | | Geometric mean (GSD) | | Personal samples collected using the Construction Occupational Health Program sampling strategy; particulate samples analysed gravimetrically; quartz analysed by Fourier transform infrared spectrophotometry; duration of sampling—6 hours of an 8-hour working day |
| | Labourers | 0.026 (5.9) | 146 | |
| | Miscellaneous trade | 0.013 (2.8) | 26 | |
| | Operating engineers | 0.007 (2.8) | 88 | |
| Flanagan *et al.* (2003)<br>Construction, USA, August 2000–January 2001 | | Geometric mean (GSD) | | Respirable samples analysed gravimetrically using NIOSH method 0600; silica analysed by Fourier transform infrared spectrophotometry using NIOSH method 7602 |
| | Clean-up, demolition with hand-held tools, concrete cutting, concrete mixing, tuck-point grinding, surface grinding, sacking and patching concrete, and concrete-floor sanding | 0.11 (5.21) | 113 | |
| Lumens & Spee (2001)<br>Construction, the Netherlands | | Geometric mean (GSD) | | Personal air samples collected during field study at 30 construction sites; duration of sampling 3 to 4 hours; gravimetric analysis of respirable dust samples; silica analysis using NIOSH method 7500 |
| | Recess miller | 0.7 (3.3) | 53 | |
| | Demolition worker | 1.1 (4.0) | 82 | |
| | Inner wall constructor | 0.04 (2.6) | 36 | |
| | Overall | 0.5 (5.6) | 171 | |

**Table 1.3 (continued)**

| Reference, industry and country, period (if reported) | Site, occupation, or exposure circumstance | Concentration of respirable crystalline silica (mg/m$^3$) | Number of samples | Comments |
|---|---|---|---|---|
| Flanagan *et al.* (2006)<br>Construction, USA, 1992–2002 | Abrasive blasters, surface and tuck point grinders, jackhammers, rock drills | Geometric mean (GSD)<br>0.13 (5.9) | 1374 | Personal silica measurements collected as part of a silica-monitoring compilation project; data provided by 3 federal or state regulatory agencies ($n$ = 827 samples), 6 university or research agencies ($n$ = 491), and 4 private consultants or contractors ($n$ = 134) |
| Akbar-Khanzadeh *et al.* (2007)<br>Construction, USA | Uncontrolled conventional grinding | Arithmetic mean<br>61.7 | 5 sessions | Personal samples collected during grinding operations in a controlled field laboratory to evaluate the effectiveness of wet grinding and local exhaust ventilation; samples collected and analysed using NIOSH methods 0600 and 7500 |
| | Wet grinding | 0.896 | 7 sessions | |
| | Local exhaust ventilation grinding | 0.155 | 6 sessions | |
| Bakke *et al.* (2002)<br>Construction, Norway, 1996–99 | Tunnel workers | Geometric mean (GSD)<br>α-Quartz, 0.035 (5.0) | 299 | Personal samples collected as part of exposure survey; sampling duration: 5 to 8 h; respirable dust analysed gravimetrically; silica analysed by NIOSH method 7500 |
| Linch (2002)<br>Construction, USA, 1992–98 | Abrasive blasting of concrete structures | TWA (8-hour)<br>2.8 | | Personal samples collected as part of NIOSH effort to characterize respirable silica exposure in construction industry; respirable dust collected and analysed according to NIOSH method 0600; silica analysed by NIOSH method 7500 |
| | Drilling concrete highway pavement | 3.3 | | |
| | Concrete-wall grinding | 0.26 | | |
| | Concrete sawing | 10.0 | | |
| | Milling of asphalt | 0.36 | | |
| Meijer *et al.* (2001)<br>Construction, USA, 1992–93 | Concrete workers | Arithmetic mean<br>0.06 | 96 | Personal samples of respirable dust and silica; gravimetric analysis of respirable dust; silica analysed by infrared spectrophotometry |
| **Miscellaneous operations** | | | | |
| Hicks & Yager (2006)<br>Coal-fired power plants, USA | Normal production activities | Arithmetic mean<br>0.048 | 108 | Personal breathing zone samples collected during normal full shifts and analysed by NIOSH method 7500 |

**Table 1.3 (continued)**

| Reference, industry and country, period (if reported) | Site, occupation, or exposure circumstance | Concentration of respirable crystalline silica (mg/m³) | Number of samples | Comments |
|---|---|---|---|---|
| Shih *et al.* (2008) | | Arithmetic mean | | Exposures measured in a municipal waste incinerator during annual furnace relining; respirable dust collected and analysed by NIOSH method 0600; silica analysed by NIOSH method 7500 |
| Furnace relining, Taiwan, China | Sandblasting | 0.578 | 7 | |
| | Bottom-ash cleaning | 0.386 | 8 | |
| | Wall demolishing | 0.116 | 8 | |
| | Relining | 0.041 | 10 | |
| | Grid repairing | 0.042 | 14 | |
| | Scaffold establishing | 0.040 | 8 | |
| | Others | 0.082 | 8 | |
| Zhuang *et al.* (2001) | | Arithmetic mean | | Special exposure survey conducted to compare results obtained from traditional Chinese samplers with nylon cyclones; gravimetric analysis of cyclone samples; silica analysis using X-ray diffraction |
| Pottery factories and metal mines, China, 1988–89 | Pottery factories | 0.116 | 54 | |
| | Iron/copper mines | 0.017 | 23 | |
| | Tin mines | 0.097 | 10 | |
| | Tungsten mines | 0.101 | 56 | |
| Yassin *et al.* (2005) | | Geometric mean (GSD) | | Analysis of personal silica measurements ($n$ = 7 209) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections |
| Several industries, USA, 1988–2003 | Soap and other detergents | 0.102 (0.757) | 6 | |
| | Testing laboratories services | 0.099 (0.896) | 53 | |
| | Cut stone and stone products | 0.091 (0.956) | 405 | |
| | General contractors | 0.091 (0.900) | 28 | |
| | Coating engraving | 0.075 (0.839) | 75 | |
| | Grey–iron foundries | 0.073 (0.877) | 1 760 | |
| | Concrete work | 0.073 (0.705) | 94 | |
| | Manufacturing explosives | 0.070 (0.841) | 9 | |
| | Bridge-tunnel construction | 0.070 (0.827) | 91 | |
| | Stonework masonry | 0.065 (0.732) | 274 | |
| | Overall | 0.073 (0.919) | 7209 | |

GM, geometric mean; GSD, geometric standard deviation; IMIS, Integrated Management Information System; NIOSH, National Institute for Occupational Safety and Health; NR, not reported; OSHA; SD, standard deviation

and 40 area samples were collected and analysed by X-ray diffraction. Personal samples were collected after the installation of local exhaust ventilation, and area samples were collected inside the industrial units before ($n$ = 20) and after ($n$ = 20) the installation of local exhaust ventilation. Personal samples were collected from process workers ($n$ = 12), hopper workers ($n$ = 8), drivers ($n$ = 11), and office employees ($n$ = 9). Personal concentrations of respirable dust were as follows: process workers, 0.21 mg/m$^3$; hopper workers, 0.45 mg/m$^3$; and, drivers, 0.20 mg/m$^3$. Personal concentrations of respirable quartz were as follows: process workers, 0.19 mg/m$^3$; hopper workers, 0.40 mg/m$^3$; and, drivers, 0.17 mg/m$^3$. Based on the area samples, the average levels of total dust and respirable dust were 9.46 mg/m$^3$ and 1.24 mg/m$^3$, respectively. The amount of free silica in the stone was 85–97%.

Golbabaei *et al.* (2004) measured TWA concentrations of total dust, respirable dust, and crystalline silica (α-quartz) in a marble stone quarry located in the north-eastern region of the Islamic Republic of Iran. Full-shift (2 × 4-hour samples) personal breathing zone samples were collected and analysed using gravimetric and X-ray diffraction methods. The highest levels of total and respirable dust exposure were observed for workers in the hammer drill process area (107.9 mg/m$^3$ and 11.2 mg/m$^3$, respectively), and the cutting machine workers had the lowest levels of exposure (9.3 mg/m$^3$ and 1.8 mg/m$^3$, respectively). The highest concentrations of α-quartz in total and respirable dust were measured in hammer drill process workers (0.670 mg/m$^3$ and 0.057 mg/m$^3$, respectively).

In a NIOSH-conducted cohort mortality study of workers from 18 silica sand plants, Sanderson *et al.* (2000) estimated historical quartz exposures using personal respirable quartz measurements (collected during 1974–96) and impinger dust samples (collected in 1946). During 1974–96, a total of 4269 respirable dust samples were collected from workers performing 143 jobs at these 18 plants. Respirable quartz concentrations ranged from less than 1 to 11700 µg/m$^3$, with a geometric mean concentration of 25.9 µg/m$^3$. Over one-third of the samples exceeded the Mine Safety and Health Administration permissible exposure limit value for quartz (PEL, 10 mg/m$^3$/(%quartz + 2)), and half of the samples exceeded the NIOSH recommended exposure limit [at the time] (REL, 0.050 mg/m$^3$). Quartz concentrations varied significantly by plant, job, and year and decreased over time, with concentrations measured in the 1970s being significantly greater than those measured later.

### *(d) Foundries*

Lee (2009) reported on exposures to benzene and crystalline silica during the inspection of a foundry processing grey and ductile iron. The facility consisted of two buildings: the main foundry where moulding, core-making, metal pouring, and shakeout took place; and, the finishing part of the site where grinding and painting was done. Personal sampling for crystalline silica was conducted in the grinding area, in casting shakeout, and in both the mould- and core-making operations. Eight-hour TWA concentrations of crystalline silica were in the range of 2.11–4.38 mg/m$^3$ in the grinding area ($n$ = 4), 1.18–2.14 mg/m$^3$ in the shakeout area ($n$ = 2), and 1.15–1.63 mg/m$^3$ in the core-maker area ($n$ = 2). The 8-hour TWA concentration in the mould area was 0.988 mg/m$^3$.

### *(e) Construction*

In a study of cement masons at six commercial building sites in Seattle, WA, USA, Croteau *et al.* (2004) measured personal exposures to respirable dust and crystalline silica during concrete-grinding activities to assess the effectiveness of a commercially available local exhaust ventilation (LEV) system. Levels were measured with and without LEV, one sample directly after the other. A total of 28 paired

samples were collected. The results showed that the application of LEV resulted in a mean exposure reduction of 92%, with the overall geometric mean respirable dust exposure declining from 4.5 to 0.14 mg/m$^3$. However, approximately one quarter of the samples collected while LEV was being used were greater than the OSHA 8–hour TWA PEL (22% of samples), and the American Conference of Governmental Industrial Hygiene (ACGIH) threshold limit value (26%) for respirable crystalline silica.

Rappaport *et al.* (2003) investigated exposures to respirable dust and crystalline silica among 80 workers in four trades (bricklayers, painters (when abrasive blasting), operating engineers, and labourers) at 36 construction sites in the Eastern and Midwestern USA. A total of 151 personal respirable air samples were collected and analysed using gravimetric and X-ray diffraction methods. Painters had the highest median exposures for respirable dust and silica (13.5 and 1.28 mg/m$^3$, respectively), followed by labourers (2.46 and 0.350 mg/m$^3$), bricklayers (2.13 and 3.20 mg/m$^3$), and operating engineers (0.720 and 0.075 mg/m$^3$). The following engineering controls and workplace characteristics were found to significantly affect silica exposures: wet dust suppression reduced labourers' exposures by approximately 3-fold; the use of ventilated cabs reduced operating engineers' exposures by approximately 6-fold; and, working indoors resulted in a 4-fold increase in labourers' exposures.

### (f) Agriculture

Archer *et al.* (2002) assessed the exposure to respirable silica of 27 farm workers at seven farms in eastern North Carolina, USA. Four-hour personal breathing zone samples ($n$ = 37) were collected during various agricultural activities and analysed for respirable dust, respirable silica, and percentage silica using gravimetric and X-ray diffraction methods. The overall mean respirable dust, respirable silica, and percentage silica values were 1.31 mg/m$^3$ ($n$ = 37), 0.66 mg/m$^3$ ($n$ = 34), and 34.4% ($n$ = 34), respectively. The highest respirable dust and respirable silica concentrations were measured during sweet potato transplanting (mean, 7.6 and 3.9 mg/m$^3$, respectively; $n$ = 5), and during riding on or driving an uncabbed tractor (mean, 3.1 and 1.6 mg/m$^3$, respectively; $n$ = 13).

Nieuwenhuijsen *et al.* (1999) measured personal exposure to dust, endotoxin, and crystalline silica during various agricultural operations at ten farms in California, USA, between April 1995 and June 1996. A total of 142 personal inhalable samples and 144 personal respirable samples were collected. The highest levels of inhalable dust exposure were measured during machine-harvesting of tree crops and vegetables (GM, 45.1 mg/m$^3$ and 7.9 mg/m$^3$, respectively), and during the cleaning of poultry houses (GM, 6.7 mg/m$^3$). Respirable dust levels were generally low, except for machine-harvesting of tree crops and vegetables (GM, 2.8 mg/m$^3$ and 0.9 mg/m$^3$, respectively). The percentage of crystalline silica was higher in the respirable dust samples (overall, 18.6%; range, 4.8–23.0%) than in the inhalable dust samples (overall, 7.4%; range, not detectable to 13.0%).

### (g) Miscellaneous operations

Harrison *et al.* (2005) analysed respirable silica dust samples ($n$ = 47) from several Chinese workplaces (three tungsten mines, three tin mines, and nine pottery mines) to determine the effect of surface occlusion by alumino-silicate on silica particles in respirable dust. The average sample percentages of respirable-sized silica particles indicating alumino-silicate occlusion of their surface were: 45% for potteries, 18% for tin mines, and 13% for tungsten mines.

To provide a more precise estimate of the quantitative relationship between crystalline silica and lung cancer, 't Mannetje *et al.* (2002) conducted a pooled analysis of existing quantitative exposure data for ten cohorts exposed to silica

(US diatomaceous earth workers; Finnish and US granite workers; US industrial sand workers; Chinese pottery workers, and tin and tungsten miners; and South African, Australian, and US gold miners). Occupation- and time-specific exposure estimates were either adopted/adapted or developed for each cohort, and converted to milligrams per cubic metre (mg/m$^3$) respirable crystalline silica. The median of the average cumulative exposure to respirable crystalline silica ranged from 0.04 mg/m$^3$ for US industrial sand workers to 0.59 mg/m$^3$ for Finnish granite workers. The cohort-specific median of cumulative exposure ranged from 0.13 mg/m$^3$–years for US industrial sand workers to 11.37 mg/m$^3$–years for Australian gold miners.

In a cross-sectional survey, Hai *et al.* (2001) determined the levels of respirable nuisance and silica dusts to which refractory brickworkers were exposed at a company in Ha Noi, Viet Nam. Respirable dust levels were in the range of 2.2–14.4 mg/m$^3$ at nine sample sites. The estimated free silica content of dust was 3.5% for unfired materials at the powder collectors ($n$ = 8 samples), and 11.4% in the brick-cleaning area following firing ($n$ = 1 sample).

Burgess (1998) investigated processes associated with occupational exposure to respirable crystalline silica in the British pottery industry during 1930–1995, and developed a quantitative job–exposure matrix. Exposure estimates were derived from 1390 air samples, the published literature, and unpublished reports of dust control innovations and process changes. In the matrix, daily 8-hour TWA airborne concentrations of respirable crystalline silica ranged from 0.002 mg/m$^3$ for pottery-support activities performed in the 1990s to 0.8 mg/m$^3$ for firing activities in the 1930s. Although exposure estimates within decades varied, median concentrations for all process categories displayed an overall trend towards progressive reduction in exposure during the 65 year span.

# 2. Cancer in Humans

## 2.1 Cancer of the lung

In the previous *IARC Monograph* (IARC, 1997) not all studies reviewed demonstrated an excess of cancer of the lung and, given the wide range of populations and exposure circumstances studied, some non-uniformity of results had been expected. However, overall, the epidemiological findings at the time supported an association between cancer of the lung and inhaled crystalline silica (α-quartz and cristobalite) resulting from occupational exposure.

The current evaluation has a primary focus on studies that employed quantitative data on occupational exposures to crystalline silica dust (α-quartz and cristobalite). The establishment of exposure–response relationships not only provides critical evidence of causation, but the availability of quantitative exposures on crystalline silica and other exposures of relevance facilitates the accurate assessment of exposure–response relationships in the presence of potential confounders. In addition to the focus on quantitative exposure–response relationships, a summary of findings from eight published meta-analyses of lung cancer was also elaborated. Of these, the seven meta-analyses involving absolute risk summarize the information from the many studies that did not consider quantitative exposure–response relationships, while the eighth is a meta-analysis of exposure-response.

Findings from cohort studies are given in Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.1.pdf, and those for the case–control studies are provided in Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.2.pdf. Given that there was concern by the previous IARC Working Group that different exposure settings (including the nature of the industry and the crystalline silica polymorph) may give rise to different (or

no) cancer risks, this evaluation is divided into sections based on the industrial setting where exposure to silica occurs. As with other evaluations, data from community-based studies are not included, although studies of persons with silicosis are.

### 2.1.1 Diatomaceous earth

Work in the diatomaceous earth industry is associated mainly with exposure to cristobalite rather than quartz, and, in the USA, is generally free of other potential confounding exposures apart from exposure to asbestos in a minority of locations. The first study of US diatomaceous earth workers revealed significant positive trends in lung cancer risk with both cumulative exposure to crystalline silica (semiquantitative) and duration of employment (Checkoway *et al.*, 1993). Owing to concerns with confounding from asbestos, estimates of asbestos exposure were developed (Checkoway *et al.*, 1996). Those with uncertain asbestos exposures were omitted from the analysis leading to the loss of seven lung cancer deaths. Among those with no asbestos exposure, the lung cancer standardized mortality ratios (SMR) for the two higher crystalline silica exposure groups were twice the magnitude of those for the two lowest exposure groups, although they were not significantly elevated. Rate ratios, with and without adjustment for asbestos exposure were very similar (within 2%), indicating that confounding due to asbestos was not an issue. Checkoway *et al.* (1997) provided findings from one of the two plants previously investigated but including 7 more years of follow-up as well as newly developed quantitative respirable crystalline silica exposures (Table 2.1 online). The lung cancer relative risks (RR) for the highest unlagged or 15-year exposure category were both significantly elevated. Trends for both unlagged and lagged exposure–response were of borderline significance. Rice *et al.* (2001) used the same cohort to examine risk, assessing the relationship between lung cancer mortality and respirable crystalline silica exposure using a variety of models. All except one model demonstrated statistical significance, and the trends of the predicted rate ratios with cumulative crystalline silica exposure were generally similar across models.

A small cohort study among Icelandic diatomaceous earth workers (Rafnsson & Gunnarsdóttir, 1997) provided findings that supported an effect of crystalline silica on lung cancer risk (SIR, 2.34; 95%CI: 0.48–6.85 for those who had worked 5 or more years). Smoking habits among the workers were reported to be similar to the general population.

### 2.1.2 Ore mining

Steenland & Brown (1995) updated a cohort of US gold miners previously studied (McDonald *et al.*, 1978; Table 2.1 online). Using quantitative estimates of cumulative exposure based on particle counts, no obvious evidence of exposure–response with lung cancer mortality was observed, nor were any of the exposure category SMRs elevated. In contrast, tuberculosis and silicosis mortality was elevated and exhibited an exposure–response relationship with crystalline silica exposure.

Gold miners were investigated in a South African cohort study (Hnizdo & Sluis-Cremer, 1991) and in case–control studies nested within that cohort study and within another South African gold miner cohort (Reid & Sluis-Cremer, 1996; Tables 2.1 and 2.2 online). In the Hnizdo & Sluis-Cremer, (1991) cohort study, lung cancer mortality was related to cumulative dust exposure when modelled as a continuous variable (respirable-surface-area–years) adjusting for smoking, as well demonstrating a monotonic increase with categories of cumulative exposures. There was also some indication of exposure–response in both case–control studies: RR, 1.12; 95%CI: 0.97–1.3 for Reid & Sluis-Cremer (1996),

and lung cancer mortality was elevated in the highest exposure group adjusting for smoking in the Hnizdo *et al.* (1997) study. [In this study, exposure to uranium did not confound the results.] [The Working Group noted the potential for confounding from radon, and also noted that the South African cohorts might overlap.]

McLaughlin *et al.* (1992) undertook a nested case–control study of lung cancer among the members of a prior cohort study by Chen *et al.* (1992) (Table 2.2 online). The study included workers from iron, copper, tungsten, and tin mines, and used quantitative estimates of crystalline silica dust and certain confounder exposures. Only tin miners showed a clear and substantial exposure–response relationship with the quantitative measures of crystalline silica cumulative exposure. The tin miners underwent further follow-up in a cohort study (Chen *et al.*, 2006) and a nested case–control study (Chen & Chen, 2002). Although the cohort study findings provided some overall indication of elevated lung cancer exposure–response mortality with cumulative dust exposure (Table 2.1 online), the findings were much less clear when presented by mine and silicosis status. In the nested case–control study (Table 2.2 online), there was evidence of exposure–response with cumulative total dust exposures. There was also evidence of a relationship between lung cancer mortality and cumulative arsenic exposure, but the high correlation between arsenic and crystalline silica levels prevented mutual adjustment, and left the etiological factor unclear. The same conclusions, more generally expressed, were reported in a simple ever/never exposed approach by Cocco *et al.* (2001), and were confirmed by Chen *et al.* (2007) adjusting for smoking and other confounding factors. Here, no relationship of lung cancer mortality with cumulative crystalline silica exposure was noted for the tungsten mines, nor was any evidence for the iron and copper mines adjusting for radon. [The Working Group noted that crystalline silica exposures were very low in the iron and copper mines.] For the tin mines, no adjustment for arsenic could be made because of its collinearity with crystalline silica exposure, but in the overall group, adjusting for smoking, arsenic, polyaromatic hydrocarbons (PAHs), and radon, no exposure–response for cumulative crystalline silica exposure emerged either by quintile or through the use of a continuous predictor. This was especially true when the iron/copper mines were removed for reason of having poorer data, when the trend tended towards lower risk with increasing crystalline silica exposure.

Carta *et al.* (2001) examined 724 compensated silicotics with radiographic indication of 1/0 or greater small opacities on the International Labor Organization scale who had worked at Sardinian lead and zinc mines, brown coal mines, and granite quarries. Using quantitative estimates of cumulative exposure to respirable crystalline silica dust and radon, the exposure–response was studied in a cohort study and a nested case–control study of 34 lung cancer cases (Tables 2.1 and 2.2 online). Little evidence of a trend with crystalline silica exposure was observed in either study component (after controlling for smoking, airflow obstruction, radon, and severity of silicosis in the case–control study). A clear relationship emerged with exposure to radon in the case–control study. [The Working Group noted that this study was small.]

### *2.1.3 Ceramics*

A case–control study of Chinese pottery workers showed evidence of elevated risk for lung cancer with exposure to crystalline silica dust, although no obvious exposure–response was seen in the three higher exposure categories (McLaughlin *et al.*, 1992; Table 2.2 online). This study was nested within the cohort analysis by Chen *et al.* (1992). Although reported exposure to asbestos was to be minimal, the workers were exposed to PAHs, and in a separate analysis

there were non-significant elevations in lung cancer risk with increasing cumulative exposure to PAHs. This was confirmed in the follow-up analysis by Chen *et al.* (2007) that found that the pottery workers had the highest PAH levels over all industrial groups. Adjustment for PAHs in the analysis led to the crystalline silica exposure relative risk of 1.1 (95%CI: 1.02–1.12) dropping to 1.0 (95%CI: 0.96–1.09). [The Working Group noted that in the prior analysis of the Chinese ceramics data by McLaughlin *et al.* (1992), adjusting for PAHs slightly raised rather than reduced the crystalline silica exposure relative risks. The correlation between the crystalline silica and PAH exposures was reported as 0.56.]

Another case–control study of pottery workers with quantitative crystalline silica dust exposures was from the United Kingdom (Cherry *et al.*, 1998). This analysis, which was restricted to ever smokers but adjusted for smoking amount and ex-smoking, showed a significantly elevated risk of lung cancer mortality with increasing average intensity of exposure, but not with cumulative exposure. No confounders, apart from smoking, were noted in this report.

Ulm *et al.* (1999) looked at workers in the German ceramics industry, as well as the stone and quarrying industry. The study was based solely on those without silicosis, as assessed using radiographic appearances. No relationship of lung cancer mortality risk with cumulative exposure, average intensity, nor peak exposure was seen in the ceramic worker subset nor overall. [The Working Group noted that the omission of those with silicosis may have restricted the range of crystalline silica exposure in the analysis leading to a loss of power to detect any relationship between crystalline silica exposure and lung cancer mortality. Moreover, the modelling included duration of exposure along with cumulative exposure, perhaps reducing the ability to detect an effect of crystalline silica exposure.]

### 2.1.4 Quarries

In an extension of the Vermont granite workers study by Costello & Graham (1988), Attfield & Costello (2004) both lengthened the follow-up from 1982 to 1994, and developed and analysed quantitative crystalline silica dust exposures (Table 2.1 online). The exposures were noteworthy for being developed from environmental surveys undertaken throughout the period of the study. However, information on smoking and silicosis status was lacking, although confounding from other workplace exposures was likely to have been minimal or non-existent. The results showed a clear trend of increasing risk of lung cancer mortality with increasing cumulative respirable crystalline silica exposure up until the penultimate exposure group. [The Working Group noted that the findings were heavily dependent on the final exposure group; when it was included, the models were no longer statistically significant.] Graham *et al.* (2004) undertook a parallel analysis of the same data as Attfield & Costello (2004), but did not use quantitative exposures, and adopted essentially the same analytical approach as in their 1998 study. They concluded that there was no evidence that crystalline silica dust exposure was a risk factor for lung cancer, their main argument being that lung cancer risks were similar by duration and tenure between workers hired pre-1940 and post-1940 – periods before and following the imposition of dust controls when the crystalline silica dust levels were very different.

As noted above, Ulm *et al.* (1999) looked at workers in the German stone and quarrying industry (includes some sand and gravel workers), as well as the ceramics industry (Table 2.2 online). The study was based solely on those without silicosis, as assessed using radiographic appearances. Neither cumulative exposure, average intensity, nor peak exposure showed a relationship with lung cancer risk in the stone and quarry worker subset, nor overall. [The Working Group noted

that the omission of those with silicosis may have restricted the range of crystalline silica exposure in the analysis leading to a loss of power to detect any relationship between crystalline silica exposure and lung cancer mortality. Moreover, the modelling included duration of exposure along with cumulative exposure, perhaps reducing the ability to detect an effect of crystalline silica exposure.] Another study of German stone and quarry workers found an excess of lung cancer (SMR, 2.40), but no relationship between lung cancer mortality and crystalline silica exposure. [The Working Group noted that the cohort study included only 440 individuals with 16 lung cancer cases. It was also restricted to those with silicosis, which was likely to lead to a lack of low exposures, a consequent limited exposure range, and low study power.]

Among studies that did not use quantitative estimates of crystalline silica exposure, that by Koskela *et al.* (1994) is of interest because it reported that the workers had little exposure to possible confounding exposures. The risk of lung cancer was significantly elevated among those with longer duration of exposure and longer latency ($P < 0.05$). Guénel *et al.* (1989) also found an excess of lung cancer among stone workers after adjustment for smoking, but this was not the case in a study of slate workers by Mehnert *et al.* (1990).

### 2.1.5 Sand and gravel

Confounding from other workplace exposures is minimal in sand and gravel operations. There are three main studies of sand and gravel workers, two in North America and one in the United Kingdom. The North American studies appear to arise from the same population of workers although there is no published information on their overlap, if any. Using the basic information from the McDonald *et al.* (2001) cohort study of nine North American sand and gravel workers, Hughes *et al.* (2001) reported significant exposure–response of lung cancer with quantitative estimates of cumulative respirable crystalline silica exposures and other related indices. McDonald *et al.* (2005) examined a slightly smaller subset of the cohort described by McDonald *et al.* (2001) based on an extended update at eight of the nine plants, and also undertook a nested case–control study. Risk of lung cancer increased monotonically with unlagged cumulative exposure ($P = 0.011$), but 15-year lagged cumulative exposures provided a slightly better fit ($P = 0.006$) (Table 2.2 online). These findings were basically similar to those obtained by Hughes *et al.* (2001) using the larger cohort and shorter follow-up time. McDonald *et al.* (2005) reported that average exposure intensity, but not years employed, showed a relationship with lung cancer risk ($P = 0.015$).

Steenland & Sanderson (2001) studied workers in 18 sand and gravel companies in the same trade organization as the nine included in the McDonald *et al.* (2001) study (Table 2.1 online). They, too, employed quantitative estimates of exposure derived from company records, and found indications of a relationship with lung cancer mortality, most strongly in the subset that had worked 6 or more months in the industry ($P < 0.06$). Further analysis using a nested case–control approach found marginal evidence of exposure–response using quartiles of cumulative exposure ($P = 0.04$), but stronger evidence with average intensity ($P = 0.003$). [The Working Group noted that a sensitivity analysis of the effect of smoking in this cohort (Steenland & Greenland, 2004) led to an adjusted overall SMR estimate of 1.43 (95% Monte Carlo limits: 1.15–1.78) compared with the original SMR of 1.60 (95%CI: 1.31–1.93). The analysis did not deal with the exposure–response estimates.]

The mortality experience of crystalline silica sand workers in the United Kingdom was evaluated by Brown & Rushton (2005b). No overall excess of lung cancer was found (although there was a large, and highly significant, variation

in lung cancer SMRs between quarries; range: 0.27–1.61, both extremes $P < 0.01$. Relative risks rose with cumulative respirable crystalline silica dust exposure in the first two quartiles, but fell below 1.0 in the highest quartile, resulting in no trend being detected. [The Working Group noted that Steenland (2005) commented that the low exposures in the Brown & Rushton (2005b) study was likely to have impacted its power to detect a crystalline-silica effect.]

### 2.1.6 Other industries

Two studies having quantitative exposures to crystalline silica remain, although both industries are known to be associated with exposure to other known or suspected lung carcinogens. The first, by Watkins *et al.* (2002) was a small case–control study focused on asphalt fumes and crystalline silica exposure. Crystalline silica exposures were low compared to most other studies, and there were no significant lung cancer elevations or trends with exposure (Table 2.2 online). The second study was a nested case–control analysis of Chinese iron and steel workers (Xu *et al.*, 1996). A significant trend with cumulative total dust exposure was reported but not for cumulative crystalline silica dust exposure, although the relative risk for the highest crystalline silica-exposed group was elevated. The findings were adjusted for smoking, but not for benzo[*a*]pyrene exposures, for which the relative risks demonstrated a clear and significant trend with cumulative exposure level.

### 2.1.7 Semiquantitative exposure and expert-opinion studies

The studies that follow used quantitative exposure measurements in deriving crystalline silica exposure estimates for individuals but ultimately converted them to exposure scores or categories in the epidemiological analysis. Hessel *et al.* (1986) undertook a case–control study of lung cancer and cumulative crystalline silica exposure in South African gold miners after coding the dust measurements to four discrete levels (0, 3, 6, 12). No exposure–response was detected. Neither was any evidence of exposure–response detected in the later necropsy study of South African gold miners (Hessel *et al.*, 1990) that used the same approach to code the exposure data. [The Working Group noted that the study methods in the case–control study may have led to overmatching for exposure in the case–control study, and that there may have been some selection bias and exposure misclassification in the second study.]

de Klerk & Musk (1998) undertook a nested case–control analysis of lung cancer within a cohort study of gold miners and showed exposure–response for log of cumulative exposure (exposure-score–years) but not for any other index of exposure. The analysis adjusted for smoking, bronchitis, and nickel exposures, and took account of asbestos exposure. The study by Kauppinen *et al.* (2003) on road pavers found a relative risk for lung cancer of 2.26 in the highest exposure group, but there was no evidence of a linear trend of risk with level of exposure. No adjustment was made for concomitant exposures to PAHs, diesel exhaust, and asbestos, nor smoking. Moulin *et al.* (2000) conducted a nested case–control study to examine lung cancer among workers producing stainless steel and metallic alloys. Their results on 54 cases and 162 controls, adjusted for smoking but not for other confounders, indicated a marginally significant evidence of a trend with increasing crystalline silica exposure as well as with PAH exposure.

Two population-based studies that involved substantial expert opinion in assigning dust levels in developing quantitative crystalline silica exposures Brüske-Hohlfeld *et al.* (2000) and Pukkala *et al.* (2005) showed an increasing risk of lung cancer with increasing crystalline silica exposure after adjustment for smoking, and in the latter study, also for social class and exposure to asbestos.

### 2.1.8 Pooled analysis, meta-analyses, and other studies

Steenland *et al.* (2001) reported on a case–control analysis nested within a pooled study of data from ten cohorts from a variety of industries and countries (Table 2.2 online). It included information on diatomaceous, granite, industrial sand, and pottery workers, and workers in tungsten, tin, and gold mines. Results from all of the studies had been previously published, although not all had originally employed quantitative estimates of crystalline silica exposure; and for half, the duration of follow-up had been extended. All indices of cumulative crystalline silica exposure (cumulative, unlagged and lagged; log cumulative, unlagged and lagged) showed highly significant trends with lung cancer risk ($P < 0.0001$), and average exposure demonstrated a less significant trend ($P < 0.05$). Of these indices, log cumulative exposure led to homogeneity in findings across the cohorts ($P = 0.08$ and 0.34 for unlagged and 15-year lag respectively). Findings were similar for the mining and non-mining subgroups. No adjustment was made for smoking and other confounders, although it was noted that smoking had previously been shown not to be a major confounder in five of the ten studies. Analyses of subsets of the data omitting cohorts with suspected other confounders (radon in South African gold mines, and arsenic or PAHs in Chinese tin miners and pottery workers) did not change the overall findings. [The Working Group noted that the robustness in the findings to exclusion of cohorts with potential confounders from other occupational exposures indicates that any confounding in the individual studies were unlikely to have had an impact on their findings related to crystalline silica.]

The presence of silicosis in an individual is a biomarker of high exposure to crystalline silica dust. Accordingly, studies of individuals with silicosis have the potential to provide useful information on the lung cancer risk associated with exposure to crystalline silica. Three meta-analyses have focused on the risk of lung cancer among individuals with silicosis (Smith *et al.*, 1995; Tsuda *et al.*, 1997; Lacasse *et al.*, 2005). Erren *et al.* (2009) also provide summary information in an electronic supplement to their article. Four others have looked at crystalline silica exposure (including silicosis status unknown and those without silicosis; Steenland & Stayner, 1997; Kurihara & Wada, 2004; Pelucchi *et al.*, 2006; Erren *et al.*, 2009). The number of studies included ranged from 11 in a meta-analysis focused on individuals without silicosis (Erren *et al.*, 2009) to 43 (Pelucchi *et al.*, 2006) in a study of those with and without silicosis. Reasons for this variation included: the publication date, the time period of interest, whether the study was focused on those with or without silicosis, the originating country of the studies, and analysis-specific criteria. For example, Steenland & Stayner (1997) rejected studies of miners and foundry workers on the assumption that they had the greatest potential for confounding exposures, and Smith *et al.* (1995) rejected certain studies they deemed under or overestimated the risk of lung cancer. Overall, of the total of 112 publications included by one or more of the seven meta-analyses, none were common to all analyses.

The detailed results from the seven meta-analyses are shown in Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.3.pdf. In brief, all analyses except for those devoted to categories without silicosis found an elevated lung cancer risk, whether occurring among those with silicosis or among crystalline-silica-exposed workers, or arising from cohort or case–control studies. [The Working Group noted that studies that restrict their analysis to individuals without silicosis potentially limit their range of crystalline silica exposure, because individuals with the highest exposures tend to be omitted. Limiting the range of exposure results in reduced power to detect associations.] Overall, the rate ratios were

very similar across studies (1.74–2.76 for those with silicosis, and 1.25–1.32 for workers exposed to crystalline silica). Results from case–control studies, where there is greater opportunity to control for smoking, revealed lower rate ratios than from cohort studies in two analyses, greater rate ratios in two, and about the same in the fifth (the sixth analysis did not break the results out separately by study type). Moreover, the supplementary materials of Erren *et al.* (2009) show equal risk for crystalline silica exposure in unadjusted and smoking-adjusted studies. The two available analyses providing results on workers exposed to crystalline silica by type of study reported larger rate ratios from the case–control studies.

A further meta-analysis examined exposure–response (Lacasse *et al.*, 2009) rather than overall risk, and for this reason its findings are reported separately. The analysis included findings from ten studies having quantitative measurements of crystalline silica exposure and adjustment for smoking. An increasing risk of lung cancer was observed with increasing cumulative exposure to crystalline silica above a threshold of 1.84 mg/m$^3$ per year. Although the overall findings were heterogeneous, they were similar to those from a subset of seven more homogeneous studies.

Many of the meta-analyses noted that a lung cancer risk was apparent either after adjusting for smoking or among non-smokers (Smith *et al.*, 1995; Tsuda *et al.*, 1997; Kurihara & Wada, 2004; Lacasse *et al.*, 2005). Yu & Tse (2007) further explored the issue of smoking on the interpretation of the published cohort and case–control studies of crystalline silica exposure and lung cancer. In this, they examined reported SMRs and standardized incidence ratios (SIR) for lung cancer reported in ten different published studies, and concluded that the risk had been systematically underreported for never smokers. After adjustment, five of the ten SMRs and SIRs showed significant lung cancer excesses among never smokers compared to two when unadjusted, and ranged from 2.60–11.93. The SMRs and SIRs for ever smokers were reduced after adjustment for smoking, but tended to retain their statistical significance.

## 2.2 Other cancers

### *2.2.1 Cancer of the stomach*

In the 40 reports with information on cancer of the stomach, 18 had relative risks > 1.0 (including three significantly elevated), and 22 with relatives risks ≤ 1.0 (including two significantly reduced).

### *2.2.2 Digestive, gastro-intestinal, or intestinal cancers*

In the 15 reports of digestive, gastro-intestinal, or intestinal cancer, seven had relative risks > 1.0 (including one significantly elevated), and eight with reltaive risks ≤ 1.0 (two significantly reduced).

### *2.2.3 Cancer of the oesophagus*

In the 14 reports of oesophageal cancer, five had relative risks > 1.0 (including three significantly elevated), and nine with relative risks ≤ 1.0.

Wernli *et al.* (2006) reported a hazard ratio of 15.80 (95%CI: 3.5–70.6) among Chinese textile workers exposed for over 10 years to crystalline silica dust. In Chinese refractory brick workers, Pan *et al.* (1999) found not only a significant elevation with being ever exposed to crystalline silica dust (RR, 2.75; 95%CI: 1.44–5.25), but also a clear exposure–response relationship with years of exposure, adjusting for smoking and other personal factors. [The Working Group noted that confounding from exposure to PAHs could not be ruled out in the above two studies.]

Yu *et al.* (2007) reported an overall SMR for cancer of the oesophagus of 2.22 (95%CI: 1.36–3.43), and an SMR of 4.21 (95%CI: 1.81–8.30)

among caisson workers (who were noted to have had higher exposures to crystalline silica dust than non-caisson workers). The relative risk of oesophageal cancer for caisson workers with silicosis was reduced to 2.34 after adjusting for smoking and alcohol drinking. No excess risk of oesophageal cancer was observed among the non-caisson workers with silicosis after adjustment.

### 2.2.4 Cancer of the kidney

In the eight reports on cancer of the kidney, five had relative risks > 1.0 (including two significantly elevated), and three with relative risks ≤ 1.0. The two with significantly elevated risks provided information on exposure–response relationships with crystalline silica exposure, although neither formally evaluated this. In US sand and gravel workers (McDonald *et al.*, 2005), a non-significant negative trend with increasing crystalline silica exposure was observed. However, in Vermont granite workers (Attfield & Costello, 2004), kidney cancer SMRs increased almost monotonically with increasing exposure (except for the last exposure group), and the SMR of 3.12 in the penultimate exposure group was significantly elevated.

### 2.2.5 Others

There have been isolated reports of excesses in other cancers but the evidence is, in general, too sparse for evaluation. Elci *et al.* (2002) reported an excess of cancer of the larynx in workers potentially exposed to crystalline silica dust, particularly for supraglottic cancer (OR, 1.8; 95%CI: 1.3–2.3), with a significant exposure–response relationship.

## 2.3 Synthesis

Findings of relevance to lung cancer and crystalline silica exposure arise from five main industrial settings: ceramics, diatomaceous earth, ore mining, quarries, and sand and gravel. Of these, the industries with the least potential for confounding are sand and gravel operations, quarries, and diatomaceous earth facilities. Among those industry segments, most studies with quantitative exposures report associations between crystalline silica exposure and lung cancer risk. The findings are supported by studies in these industries that lack quantitative exposures. Results from the other industry segments generally added support although some studies had potential confounding from arsenic, radon, or PAHs. In one case among Chinese tin miners, the arsenic and crystalline silica exposures were virtually collinear, and no adjustment could be made for arsenic. In another (Chinese pottery workers), adjustment for PAHs removed a significant crystalline silica exposure effect, and in a third, among iron and copper miners, the crystalline silica effect disappeared after adjustment for radon. In these, the role of crystalline silica exposure must be regarded as unclear. Mixed findings were reported among gold, tungsten, and lead/zinc miners.

The strongest evidence supporting the carcinogenicity of crystalline silica in the lung comes from the pooled and meta-analyses. The pooled analysis demonstrated clear exposure–response, while all of the meta-analyses strongly confirmed an overall effect of crystalline silica dust exposure despite their reliance on different studies in coming to their conclusions.

Cancers other than that of the lung have not been as thoroughly researched. In many cases the findings were reported in passing, in analyses focused on lung cancer, and rarely have the data examined exposure–response with crystalline silica exposure or its surrogates.

## 3. Cancer in Experimental Animals

No additional relevant cancer bioassays have been conducted since the previous *IARC Monograph* (IARC, 1997) except for a study in hamsters by inhalation (Muhle *et al.*, 1998), and a study in mice by intratracheal instillation (Ishihara *et al.*, 2002). Studies from the previous evaluation considered adequate are summarized below together with the new studies published since.

### 3.1 Inhalation exposure

See Table 3.1

#### *3.1.1 Mouse*

Female BALB/cBYJ mice exposed to crystalline silica by inhalation (Wilson *et al.*, 1986) did not have an increase in lung tumours compared to controls. Pulmonary adenomas were observed in both the silica-exposed (9/60) and the control animals (7/59). [The Working Group noted that the study groups were small (6–16 mice).]

#### *3.1.2 Rat*

Male and female F344 rats were exposed to 0 or 52 mg/m$^3$ of crystalline silica (Min-U-Sil) over a 24-month period. Interim removals of ten males and ten females per group were made after 4, 8, 12, and 16 months of exposure. Half of those removed were necropsied, and half were held until the end of the 24 months. None of the controls developed a lung tumour. In the silica-exposed rats, the first pulmonary tumour appeared at 494 days, and the incidence was 10/53 in females and 1/47 in males (Dagle *et al.*, 1986).

One group of 62 female F344 rats was exposed by nose-only inhalation to 12 mg/m$^3$ crystalline silica (Min-U-Sil) for 83 weeks. An equal number of controls was sham-exposed to filtered air, and 15 rats were left untreated. The animals were observed for the duration of their lifespan. There were no lung tumours in the sham-exposed group, and 1/15 unexposed rats had an adenoma of the lung. In the quartz-exposed rats, the incidence of lung tumours was 18/60 (Holland *et al.*, 1983, 1986; Johnson *et al.*, 1987).

Groups of 50 male and 50 female viral antibody-free SPF F344 rats were exposed by inhalation to 0 or 1 mg/m$^3$ silica (DQ12; 87% crystallinity as quartz) for 24 months. The rats were then held for another 6 weeks without exposure. The incidence of lung tumours in the silica-exposed rats was 7/50 males and 12/50 in females. Only 3/100 controls had lung tumours (Muhle *et al.*, 1989, 1991, 1995).

Three groups of 90 female Wistar rats, 6–8 weeks old, were exposed by nose-only inhalation to 6.1 or 30.6 mg/m$^3$ DQ12 quartz for 29 days. Interim sacrifices were made immediately after the exposure and at 6, 12, and 24 months, with the final sacrifice at 34 months after exposure. The total animals with lung tumours was 0 (controls), 37/82 (low dose), and 43/82 (high dose). Many animals had multiple tumours (Spiethoff *et al.*, 1992).

#### *3.1.3 Hamster*

Groups of 50 male and 50 female Syrian golden hamsters were exposed to 0 (control) or 3 mg/m$^3$ DQ12 quartz (mass median aerodynamic diameter, 1.3 µm) for 18 months. The experiment was terminated 5 months later. In the silica-exposed group, 91% of the animals developed very slight to slight fibrosis in the lung, but no significant increase of lung tumours was observed (Muhle *et al.*, 1998)

## Table 3.1 Studies of cancer in experimental animals exposed to crystalline silica (inhalation exposure)

| Species, strain (sex)<br>Duration<br>Reference | Dosing regimen<br>Animals/group at start<br>Particle size, GSD | Incidence of tumours in respiratory tract | Significance | Comments |
|---|---|---|---|---|
| Mouse, BALB/c BYJ (F)<br>150, 300 or 570 d<br>Wilson *et al.* (1986) | 0, 1.5, 1.8 or 2.0 mg/m$^3$<br>8 h/d, 5 d/wk<br>6–16 animals<br>Diameter < 2.1 µm | Lung (adenomas):<br>7/59 (control), 9/60 (all exposed) | [NS] | |
| Rat, F344 (M, F)<br>24 mo<br>Dagle *et al.* (1986) | 0, 52 mg/m$^3$<br>6 h/d, 5 d/wk<br>72/sex<br>MMAD, 1.7–2.5 µm; GSD, 1.9–2.1 | Lung (epidermoid carcinomas):<br>M–0/42 (control), 1/47<br>F–0/47 (control), 10/53 | [NS]<br>[$P < 0.002$] | |
| Rat, F344 (F)<br>Lifespan<br>Holland *et al.* (1983, 1986); Johnson *et al.* (1987) | 0, 12 mg/m$^3$<br>6 h/d, 5 d/wk for 83 wk<br>62 animals<br>MMAD, 2.24 µm; GSD, 1.75 | Lung (tumours):<br>0/54 (control), 18/60<br>(11 adenocarcinomas, 3 squamous cell carcinomas, 6 adenomas) | [$P < 0.001$] | Nose-only inhalation exposure. Age unspecified |
| Rat, SPF F344 (M, F)<br>30 mo<br>Muhle *et al.* (1989, 1991, 1995) | 0, 1 mg/m$^3$<br>6 h/d, 5 d/wk for 24 mo<br>50/sex<br>MMAD, 1.3 µm; GSD, 1.8 | Lung (tumours):<br>3/100 (control M, F), 7/50 (M), 12/50 (F)<br>M–1 adenoma, 3 adenocarcinomas, 2 benign cystic keratinizing squamous cell tumours, 1 adenosquamous carcinoma, 1 squamous cell carcinoma<br>F–2 adenomas, 8 adenocarcinomas, 2 benign cystic keratinizing squamous cell tumours | Unspecified (M)<br>[$P < 0.05$] (F) | |
| Rat, Wistar (F)<br>Up to 35 mo<br>Spiethoff *et al.* (1992) | 0, 6.1, 30.6 mg/m$^3$<br>6 h/d, 5 d/wk for 29 d<br>90 animals<br>MMAD, 1.8 µm; GSD, 2.0 | 0/85 (control), 37/82 (low dose), 43/82 (high dose)<br>Multiple tumours/rat:<br>21 bronchiolo-alveolar adenomas,<br>43 bronchiolo-alveolar carcinomas,<br>67 squamous cell carcinomas, 1 anaplastic carcinoma | [$P < 0.0001$]<br>(both doses) | Nose-only inhalation exposure |

d, day or days; F, female; GSD, geometric standard deviation; h, hour or hours; M, male; MMAD, mass median aerodynamic diameter; mo, month or months; NS, not significant; wk, week or weeks

## 3.2 Intranasal administration

### 3.2.1 Mouse

Two groups of 40 female (C57xBALB/c) $F_1$ mice received a single intranasal instillation of 4 mg of synthetic *d*- or *l*-quartz. A group of 60 females received an intranasal instillation of saline. Survivors were killed at 18 months after treatment, and the incidence of lymphomas and leukaemias combined was 0/60 (controls), 2/40 (*d*-quartz), and 6/40 (*l*-quartz) (Ebbesen, 1991). [The Working Group noted that the study was not designed to detect silica-induced lung tumours, and also noted the lack of information on quartz retention.]

## 3.3 Intratracheal administration

See Table 3.2

### 3.3.1 Mouse

A group of 30 male A/J mice, 11–13 weeks old, received weekly intratracheal instillations of 2.9 mg quartz for 15 weeks. A group of 20 mice received instillations of vehicle [unspecified]. Animals were killed 20 weeks after the instillations. The incidences of lung adenomas were 9/29 in the controls, and 4/20 for the silica-instilled mice, values that were not statistically different (McNeill *et al.*, 1990).

Ishihara *et al.* (2002) administered a single dose (2 mg in saline/mouse) of crystalline silica to a group of four C57BL/6N mice by intratracheal instillation to study subsequent genotoxic effects. A control group of four animals was instilled saline only. Silicotic lesions were observed in the lungs of the exposed mice, but no pulmonary neoplasms were observed after 15 months.

### 3.3.2 Rat

A group of 40 Sprague Dawley rats [sex unspecified] received weekly instillations of 7 mg quartz (Min-U-Sil) in saline for 10 weeks. Another groups of 40 rats received instillations of saline alone, and 20 rats remained untreated. Animals were observed over their lifespan. The incidence of lung tumours in quartz-treated rats was 6/36, 0/40 in the saline controls, and 0/18 in the untreated rats (Holland *et al.*, 1983).

Groups of 85 male F344 rats received a single intratracheal instillation of 20 mg quartz in deionized water, Min-U-Sil or novaculite, into the left lung. Controls were instilled with vehicle only. Interim sacrifices of ten rats were made at 6, 12, and 18 months with a final sacrifice at 22 months. The incidence of lung tumours in the Min-U-Sil-instilled rats was 30/67, in the novaculite-treated rats 21/72, and in controls 1/75. All of the lung tumours were adenocarcinomas, except for one epidermoid carcinoma in the novaculite-treated rats (Groth *et al.*, 1986).

Groups of male and female F344/NCr rats [initial number unspecified] received one intratracheal instillation of 12 or 20 mg quartz in saline or 20 mg of ferric oxide (non-fibrogenic dust) in saline. Interim sacrifices were made at 11 and 17 months with a final sacrifice at 26 months. There was a group of untreated controls observed at unscheduled deaths after 17 months. No lung tumours were observed in the ferric-oxide-treated rats and only one adenoma was observed in the untreated controls. The high incidences of benign and mainly malignant lung tumours observed in the quartz-treated rats is summarized in Table 3.3 (Saffiotti, 1990, 1992; Saffiotti *et al.*, 1996).

Six groups of 37–50 female Wistar rats, 15 weeks old, received either a single or 15 weekly intratracheal instillation of one of three types of quartz preparations in saline (see Table 3.4). A control group received 15 weekly instillations of saline. To retard the development of silicosis,

## Table 3.2 Studies of cancer in experimental animals exposed to silica (intratracheal instillation)

| Species, strain (sex)<br>Duration<br>Reference | Dosing regimen<br>Animals/group at start<br>Particle size | Incidence of tumours | Significance |
|---|---|---|---|
| Mouse, A/J (M)<br>20 wk<br>McNeill *et al.* (1990) | 0, 2.9 mg<br>Weekly for 15 wk<br>30, 20 (controls)<br>1–5 µm (size not further specified) | Lung (adenomas):<br>9/29 (control), 4/20<br>Tumour multiplicity: 0.31 ± 0.09 (control), 0.20 ± 0.09 | [NS]<br>[NS] |
| Rat, Sprague Dawley (NR)<br>Lifespan<br>Holland *et al.* (1983) | 0 (saline), 7 mg<br>Weekly for 10 wk<br>40 animals<br>1.71 ± 1.86 µm | Lung (1 adenoma, 5 carcinomas):<br>0/40 (control), 6/36 | [$P$<0.05] (carcinomas) |
| Rat, F344 (M)<br>22 mo<br>Groth *et al.* (1986) | 0, 20 mg once only<br>85 animals < 5 µm | Lung (adenocarcinomas):<br>1/75 (control), 30/67 | [$P$<0.001] |
| Rat, F344/NCr (M, F)<br>11, 17 or 26 mo<br>Saffiotti (1990, 1992); Saffiotti *et al.* (1996) | 0, 12, 20 mg quartz<br>Once only<br>Ferric oxide (20 mg) was negative control<br>[Initial number of rats, NR]<br>0.5–2.0 µm | High incidences of benign and mainly malignant lung tumours in quartz-treated rats reported in Table 3.3<br>No tumours observed in ferric oxide group<br>One adenoma in untreated controls | NR |
| Rat, Wistar<br>Lifespan<br>Pott *et al.* (1994) | 0 (saline), one single or 15 weekly injections of one of 3 types of quartz<br>Some rats received PVNO to protect against silicosis<br>37–50/group | Incidences of benign and malignant lung tumours in quartz-treated rats are shown in Table 3.4<br>No tumours observed in saline-treated rats | NR |
| Hamster Syrian Golden (NR)<br>Lifespan<br>Holland *et al.* (1983) | 0 (saline), 3, 7 mg quartz (Min-U-Sil)<br>Once a wk for 10 wk<br>48/group; 68 (controls)<br>1.71 ± 1.86 µm | No lung tumours in any group | |
| Hamster, Syrian Golden (M)<br>Lifespan<br>Renne *et al.* (1985) | 0 (saline), 0.03, 0.33, 3.3, or 6.0 mg quartz (Min-U-Sil) weekly for 15 wk<br>25–27/group<br>MMAD, 5.1 µm<br>Geometric diameter, 1.0 µm | No lung tumours in any group | |
| Hamster, Syrian Golden (M)<br>92 wk<br>Niemeier *et al.* (1986) | 0 (saline), 1.1 (Sil-Co-Sil) or 0.7 (Min-U-Sil) mg<br>One group received 3 mg ferric oxide<br>50/group<br>5 µm (Min-U-Sil) | No tumours in saline controls or in Sil-Co-Sil groups<br>1 adenosquamous carcinoma of the bronchi and lung in Min-U-Sil group and 1 benign tumour of the larynx in ferric oxide group | |

M, male; MMAD, mass median aerodynamic diameter; mo, month or months; NR, not reported; NS, not significant; PVNO, polyvinylpyridine-*N*-oxide; wk, week or weeks

**Table 3.3 Incidence, numbers, and histological types of lung tumours in F344/NCr rats after a single intratracheal instillation of quartz**

| Treatment | | Observation time | Lung tumours | |
|---|---|---|---|---|
| **Material** | **Dose[a]** | | **Incidence** | **Types** |
| **Males** | | | | |
| Untreated | None | 17–26 mo | 0/32 | |
| Ferric oxide | 20 mg | 11–26 mo | 0/15 | |
| Quartz (Min-U-Sil 5) | 12 mg | Killed at 11 mo | 3/18 (17%) | 6 adenomas, 25 adenocarcinomas, 1 undifferentiated carcinoma, 2 mixed carcinomas, 3 epidermoid carcinomas |
| | | Killed at 17 mo | 6/19 (32%) | |
| | | 17–26 mo | 12/14 (86%) | |
| Quartz (HF-etched Min-U-Sil 5) | 12 mg | Killed at 11 mo | 2/18 (11%) | 5 adenomas, 14 adenocarcinomas, 1 mixed carcinoma |
| | | Killed at 17 mo | 7/19 (37%) | |
| | | 17–26 mo | 7/9 (78%) | |
| **Females** | | | | |
| Untreated | None | 17–26 mo | 1/20 (5%) | 1 adenoma |
| Ferric oxide | 20 mg | 11–26 mo | 0/18 | |
| Quartz (Min-U-Sil 5) | 12 mg | Killed at 11 mo | 8/19 (42%) | 2 adenomas, 46 adenocarcinomas, 3 undifferentiated carcinomas, 5 mixed carcinomas, 3 epidermoid carcinomas |
| | | Killed at 17 mo | 10/17 (59%) | |
| | | 17–26 mo | 8/9 (89%) | |
| | 20 mg | 17–26 mo | 6/8 (75%) | 1 adenoma, 10 adenocarcinomas, 1 mixed carcinoma, 1 epidermoid carcinoma |
| Quartz (HF-etched Min-U-Sil 5) | 12 mg | Killed at 11 mo | 7/18 (39%) | 1 adenoma, 36 adenocarcinomas, 3 mixed carcinomas, 5 epidermoid carcinomas |
| | | Killed at 17 mo | 13/16 (81%) | |
| | | 17–26 mo | 8/8 (100%) | |

[a] Suspended in 0.3 or 0.5 mL saline

HF, hydrogen fluoride; mo, month or months

From Saffiotti (1990, 1992), Saffiotti *et al.* (1996)

**Table 3.4 Incidence, numbers, and histological types of lung tumours in female Wistar rats after intratracheal instillation of quartz**

| Material | Surface area | No. of instillations | No. of rats examined | No. and #% of rats with primary epithelial lung tumours[a] | | | | | Other tumours[b] |
|---|---|---|---|---|---|---|---|---|---|
| | ($m^2$/g) | (del # × mg) | | Adenoma | Adenocarcinoma | Benign CKSCT | Squamous cell carcinoma | Total (%) | |
| Quartz (DQ 12) | 9.4 | 15 × 3 | 37 | 0 | 1z | 11 | 1 + 1y | 38 | 1 |
| Quartz (DQ 12) + PVNO | 9.4 | 15 × 3 | 38 | 0 | 1 + 3z | 8 + 1x | 4+1x+3y+1z | 58 | 2 |
| Quartz (DQ 12) | 9.4 | 1 × 45 | 40 | 0 | 1 | 7 | 1 | 23 | 2 |
| Quartz (Min-U-Sil) | – | 15 × 3 | 39 | 1 | 4 + 4z | 6 | 1+2y+2z+1y,z | 54 | 3 |
| Quartz (Min-U-Sil) + PVNO | – | 15 × 3 | 35 | 1 | 2 + 1x | 8 | 5+1x+1y+1z | 57 | 3 |
| Quartz Sykron (F 600) | 3.7 | 15 × 3 | 40 | 0 | 3 | 5 | 3 + 1z | 30 | 1 |
| 0.9% Sodium chloride | – | 15 × 0.4 mL | 39 | 0 | 0 | 0 | 0 | 0 | 5 |

[a] If an animal was found to bear more than one primary epithelial lung tumour type, this was indicated as follows: [x]adenoma; [y]adenocarcinoma; [z]benign CKSCT.

[b] Other types of tumours in the lung: fibrosarcoma, lymphosarcoma, mesothelioma or lung metastases from tumours at other sites

PVNO, polyvinylpyridine-*N*-oxide; CKSCT, cystic keratinizing squamous cell tumour

From Pott *et al.* (1994)

two of the groups received injections of polyvinylpyridine-*N*-oxide. All groups of quartz-exposed rats had a significant increase in lung tumours, and the rats protected against silicosis developed more pulmonary squamous cell carcinomas than rats that were not protected (Pott *et al.*, 1994).

### 3.3.3 Hamster

Two groups of 48 Syrian hamsters [sex unspecified] received intratracheal instillations of 3 or 7 mg quartz (Min-U-Sil) in saline once a week for 10 weeks. A group of 68 hamsters received saline alone, and another group of 72 hamsters were untreated. All animals were observed for their lifespan. No lung tumours were observed in any of the groups (Holland *et al.*, 1983).

Groups of 25–27 male Syrian golden hamsters, 11–weeks old, received weekly intratracheal instillation of 0.03, 0.33, 3.3, or 6.0 mg quartz (Min-U-Sil) in saline for 15 weeks. Groups of 27 saline-instilled hamsters and 25 untreated controls were used as controls. Animals were observed for their lifespan. No lung tumours were observed in any group (Renne *et al.*, 1985).

Three groups of 50 male Syrian golden hamsters received weekly instillations of 1.1 mg of quartz as Sil-Co-Sil, or 0.7 mg of quartz as Min-U-Sil, or 3 mg of ferric oxide (non-fibrogenic particle) in saline for 15 weeks. A group of 50 saline-instilled hamsters served as controls. Survivors were killed at 92 weeks after the beginning of the instillations. No respiratory tract tumours were observed in the hamsters exposed to Sil-Co-Sil or in the saline controls. One adenosquamous carcinoma of the bronchi and lung was observed in the Min-U-Sil group, and one benign tumour of the larynx in the ferric-oxide-exposed group (Niemeier *et al.*, 1986).

## 3.4 Intrapleural and intrathoracic administration

### 3.4.1 Mouse

One mouse study was reported in the previous *IARC Monograph* (IARC, 1997) in which the route of exposure was via a single intrathoracic injection of tridymite. The study was only reported as an abstract, and therefore is not described here (Bryson *et al.*, 1974).

### 3.4.2 Rat

Two groups of 48 male and 48 female standard Wistar rats and two groups 48 male and 48 female SPF Wistar rats were given a single intrapleural injection of 20 mg alkaline-washed quartz (size, < 5 μm) in saline, and observed for their lifespan. Control rats received injections of 0.4 mL saline alone. Malignant tumours of the reticuloendothelial system involving the thoracic region were observed in 39/95 quartz-treated SPF rats [$P < 0.001$] (23 histiocytic lymphomas, five Letterer-Siwe/Hand-Schüller-Christian disease-like tumours, one lymphocytic lymphoma, four lymphoblastic lymphosarcomas, and six spindle cell sarcomas), and in 31/94 quartz-treated standard rats [$P < 0.001$] (30 histiocytic lymphomas and one spindle-cell sarcoma). In the SPF control animals, 8/96 rats had tumours (three lymphoblastic lymphosarcomas, five reticulum cell sarcomas), 7/85 standard rat controls had tumours (one lymphoblastic lymphosarcoma, and six reticulum cell sarcomas) (Wagner & Berry, 1969; Wagner, 1970; Wagner & Wagner, 1972). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

In a second study, with the same dosing regimen and type of quartz, 23 rats developed malignant reticuloendothelial system tumours (21 malignant lymphomas of the histiocytic type [MLHT], two thymomas, and one lymphosarcoma/thymoma/spindle cell sarcoma) in 80 male

and 80 female SPF Wistar rats after 120 weeks. In another experiment, 16 male and 16 female SPF Wistar rats dosed similarly with Min-U-Sil quartz were observed until they were moribund. Eight of the 32 rats developed MLHT and three developed thymomas/lymphosarcomas. In a last experiment with the same experimental design, 18 of 32 SPF Wistar rats that had been injected with cristobalite developed malignant lymphomas (13 MLHT and five thymomas/lymphosarcomas). No MLHT and one thymoma/lymphosarcoma tumours were observed in 15 saline-injected control rats. (Wagner, 1976). [The Working Group noted that the distribution of tumours over sexes was unspecified, and that no statistics were provided.]

In one experiment, groups of 16 male and 16 female Wistar rats were given intrapleural injections of 20 mg of four types of quartz (Min-U-Sil, D&D, Snowit, and DQ12). The animals were observed for their lifespan. For all but the group treated with DQ12 quartz, there was a statistically significant increase in MLHT over saline controls (Table 3.5). In a second experiment with the same experimental design, two other strains of rats were injected Min-U-Sil (12 male and 12 female PVG rats and 20 male and 20 female Agus rats). A non-significant increase in MLHT was observed in both strains, and there was no MLHT in the saline controls. In a third experiment with the same experimental design, cristobalite was injected, and 4/32 treated Wistar rats developed MLHT [not significant], but none of the 32 saline controls did. In a final experiment, 16 male and 16 female Wistar rats were injected triolymite (size, < 0.5 μm; $0.35 \times 10^6$ particle/μg), and observed for their lifespan. A total of 16/32 Wistar rats developed MLHT, whereas no such tumours were observed in the 32 saline controls (Wagner *et al.*, 1980). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

Two groups of 36 2-month-old male Sprague-Dawley rats, received a single intrapleural injection of 20 mg DQ12 quartz in saline or saline alone, and were observed for their lifespan. Twenty-seven male rats served as untreated controls. Six malignant histiocytic lymphomas and two malignant Schwannomas were observed in the quartz-treated group [not significant], and one chronic lymphoid leukaemia and one fibrosarcoma were observed in the saline group and untreated controls, respectively (Jaurand *et al.*, 1987).

## 3.5 Intraperitoneal administration

### *3.5.1 Rat*

Two groups of 16 male and 16 female SPF Wistar rats received a single intraperitoneal injection of 20 mg of Min-U-Sil quartz in saline, and were observed for their lifespan. There were 12 saline controls [sex unspecified]. A total of 9/64 quartz-exposed rats developed malignant lymphomas (two MLHT and seven thymoma/lymphosarcomas). None of the saline controls developed MLHT, but one thymoma/lymphosarcoma was noted (Wagner, 1976). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

## 3.6 Subcutaneous administration

### *3.6.1 Mouse*

Two groups of 40 female (C57xBALB/c) $F_1$ mice received a single subcutaneous injection of 4 mg of *d*- or *l*-quartz. A group of 60 female mice served as saline controls. At 18 months after injection, there was an incidence of lymphomas/leukemias of 0/60, 1/40 and 12/40 ($P < 0.001$), and of liver adenomas of 0/60, 1/40 and 3/40 for the saline controls, *d*-quartz and *l*-quartz groups, respectively. No injection-site tumours were reported (Ebbesen, 1991).

**Table 3.5 Incidences of malignant lymphoma of the histiocytic type (MLHT) in Wistar rats after an intrapleural injection of 20 mg quartz/animal**

| Sample | No. of particles × $10^6$/µg | Size distribution (%) | | | Mean survival (days) | Incidence of MLHT (%)[a] |
|---|---|---|---|---|---|---|
| | | < 1 µm | 1–2 µm | 2–4.6 µm | | |
| Min-U-Sil (a commercially prepared crystalline quartz probably 93% pure) | 0.59 | 61.4 | 27.9 | 9.1 | 545 | 11/32 (34%)b |
| D&D (obtained from Dowson & Dobson, Johannesburg, pure crystalline quartz) | 0.30 | 48.4 | 33.2 | 18.4 | 633 | 8/32 (25%)b |
| Snowit (commercially prepared washed crystals) | 1.1 | 81.2 | 12.9 | 5.6 | 653 | 8/32 (25%)b |
| DQ12 (standard pure quartz) | 5.0 | 91.4 | 7.8 | 0.8 | 633 | 5/32 (16%) |
| Saline controls | – | – | – | – | 717 | 0 [0/32] (0%) |

[a] Sex unspecified

[b] [Significantly different from controls by Fisher Exact test, $P < 0.05$]

From Wagner *et al.* (1980)

## 3.7 Intravenous administration

### *3.7.1 Mouse*

Groups of 25 male and 25 female strain A mice were injected in the tail vein with 1 mg quartz in 0.1 mL of saline, with a control group of 75 male and female untreated animals. Animals were killed 3, 4.5 or 6 months after injection. There was no difference in the incidences and multiplicities of pulmonary adenomas between treated and untreated animals (Shimkin & Leiter, 1940).

## 3.8 Administration with known carcinogens

### *3.8.1 Inhalation*

#### *(a) Rat*

Studies have been completed to determine the effect of co-exposure to silica and Thorotrast, a known carcinogen (See Table 3.6). Two sets of three groups of 90 female Wistar rats, 6–8 weeks old, were exposed by inhalation to 0, 6, or 31 mg/m$^3$ of DQ12 quartz (mass median diameter, 1.8 µm; GSD, 2.0) for 6 hours/day 5 days/week for 29 days. One week after the inhalation exposure, one group of quartz-exposed rats and one group of sham-exposed rats received an intravenous injection of Thorotrast (2960 Bq $^{228}$Th/mL, 0.6 mL). Controls were only sham-exposed. In each of the six groups, interim sacrifices of three or six animals each were made 0, 6, 12 and 24 months after the end of exposure. The experiment was terminated 34 months after the end of exposure. In rats that were exposed to silica by inhalation and then given Thorotrast, there was a small increase in lung tumours compared to the already high incidence of benign and malignant tumours induced by silica alone (Spiethoff *et al.*, 1992).

### *3.8.2 Intratracheal administration*

#### *(a) Rat*

Four groups of white rats (group sizes varied from 28 to 70, with approximately equal numbers of males and females) were given either no treatment or a single instillation of 5 mg benzo[*a*]pyrene or an instillation of 50 mg quartz (size, 82% < 2 µm) and 5 mg benzo[*a*]pyrene (Group A) or 50 mg quartz and a later (1 month) instillation of 5 mg benzo[*a*]pyrene (Group B). The rats were observed until death. There were no

**Table 3.6 Incidence, numbers and histological types of lung tumours in female Wistar rats after inhalation exposure to quartz and/or Thorotrast**

| Treatment | Number of rats[a] | Lung tumours | | | | |
|---|---|---|---|---|---|---|
| | | Incidence | Total number | Histological type | | |
| | | Observed | | Bronchiolo-alveolar adenoma | Bronchiolo-alveolar carcinoma | Squamous cell carcinoma |
| Controls | 85 | – | – | – | – | – |
| Low-dose quartz | 82 | 37 | 62 | 8 | 17 | 37 |
| High-dose quartz | 82 | 43 | 69 | 13 | 26 | 30 |
| Thorotrast (Tho) | 87 | 3 | 6 | – | 5 | 1 |
| Low-dose quartz + Tho | 87 | 39 | 68 | 10 | 28 | 30 |
| High-dose quartz + Tho | 87 | 57 | 98 | 16 | 47 | 35 |

[a] Without the animals sacrificed 0 and 6 months after the end of inhalation exposure.
From Spiethoff *et al.* (1992)

lung tumours in the untreated rats (0/45), nor in those exposed to benzo[*a*]pyrene alone (0/19). In the combined exposures to benzo[*a*]pyrene and quartz, an increased incidence in lung tumours was observed (Group A, 14/31, 11 squamous cell carcinomas and three papillomas; Group B, 4/18, two papillomas and two carcinomas) (Pylev, 1980). [The Working Group noted the absence of a group exposed to quartz alone.]

### *(b) Hamster*

Groups of 50 male Syrian golden hamsters received weekly intratracheal instillations for 15 weeks in saline of 3 mg benzo[*a*]pyrene or 3 mg ferric oxide or 3 mg ferric oxide plus 3 mg benzo[*a*]pyrene or 1.1 mg Sil-Co-Sil or 1.1 mg Sil-Co-Sil plus 3 mg benzo[*a*]pyrene or 0.7 mg Min-U-Sil or 0.7 mg Min-U-Sil plus 3 mg benzo[*a*]pyrene or 7 mg Min-U-Sil or 7 mg Min-U-Sil plus 3 mg benzo[*a*]pyrene. Fifty male controls received saline alone. Survivors were killed at 92 weeks after exposure. Co-exposures with silica caused an enhancement of the number of respiratory tract tumours induced by benzo[*a*]pyrene (mainly in the bronchus and lung) (Niemeier *et al.*, 1986; Table 3.7).

## 3.9 Synthesis

Studies of the carcinogenicity of crystalline silica in experimental animal models have shown quartz dust to be a lung carcinogen in rats following inhalation and intratracheal instillation, but not in mice or hamsters. Rats are known to be more sensitive than are mice or hamsters to the induction of lung tumours due to other inhaled poorly soluble particles, such as carbon black (Mauderly *et al.*, 1994).

Quartz-induced lymphoma incidence was also increased in several experiments in rats after intrapleural administration, and in one study in mice after subcutaneous administration. Tridymite- and cristobalite-induced lymphomas were observed in only a single experiment.

**Table 3.7 Incidences of respiratory tract tumours in Syrian golden hamsters after intratracheal administration of quartz with or without benzo[*a*]pyrene**

| Treatment | No. of animals | No. of animals with respiratory tract tumours | No. of respiratory tract tumours[a] by site | | | Mean latency (wk) |
|---|---|---|---|---|---|---|
| | | | Larynx | Trachea | Bronchus and lung | |
| Saline control | 48 | 0 | 0 | 0 | 0 | – |
| BaP | 47 | 22 | 5 | 3 | 32 | 72.6 |
| Ferric oxide | 50 | 1 | 1 | 0 | 0 | 62 |
| Ferric oxide + BaP | 48 | 35b,c | 5 | 6 | 69 | 70.2 |
| Sil-Co-Sil | 50 | 0 | 0 | 0 | 0 | – |
| Sil-Co-Sil + BaP | 50 | 36b,c | 13 | 13 | 72 | 66.5 |
| Min-U-Sil | 50 | 1 | 0 | 0 | 1 | 68 |
| Min-U-Sil + BaP | 50 | 44b,c | 10 | 2 | 111 | 68.5 |
| Min-U-Sil + ferric oxide | 49 | 0 | 0 | 0 | 0 | – |
| Min-U-Sil + ferric oxide + BaP | 50 | 38b,c | 10 | 4 | 81 | 66.7 |

[a] Types of tumours: polyps, adenomas, carcinomas, squamous cell carcinomas, adenosquamous carcinomas, adenocarcinomas, sarcomas.
[b] Statistically significantly higher ($P < 0.00001$; two-tailed Fisher Exact test) compared with the corresponding group not treated with BaP.
[c] Statistically significantly higher ($P < 0.01$; two-tailed Fisher Exact test) compared with the BaP group.
BaP, benzo[*a*]pyrene
From Niemeier *et al.* (1986)

# 4. Other Relevant Data

## 4.1 Deposition and biopersistence

The inhalation of crystalline silica is associated with various lung diseases including acute silicosis or lipoproteinosis, chronic nodular silicosis, and lung cancer. Exposure to silica dust may also cause renal and autoimmune diseases (Steenland & Goldsmith, 1995; Stratta *et al.*, 2001; Cooper *et al.*, 2002; Otsuki *et al.*, 2007). In silicotic patients, alveolar macrophages collected by pulmonary lavage contain crystalline silica and at autopsy, elevated levels of quartz are found in the lungs and lymph nodes. Crystalline silica is poorly soluble and biopersistent; even after cessation of exposure, silicosis can progress and is a risk factor for the development of lung cancer (IARC, 1997).

Alveolar macrophages play a key role in silica-related toxicity, and therefore the cytotoxic potency of silica particles determine the degree of silica-related pathogenicity (IARC, 1997; Donaldson & Borm, 1998). The stronger the cytotoxicity of crystalline silica to alveolar macrophages, the higher the intensity of the inflammatory reaction, and the longer the residence time of the particle in the lung (Donaldson & Borm, 1998; Fenoglio *et al.*, 2000a).

Rodent inhalation studies have investigated the relationship between intrinsic particle toxicity, persistent inflammation, altered macrophage-mediated clearance, and biopersistence in the lung (Warheit *et al.*, 2007). Crystalline silica particles induce lung inflammation that persists even after cessation of exposure, with alveolar macrophages having reduced chemotactic responses and phagocytosis. Crystalline silica impairs macrophage-mediated clearance secondary to its cytotoxicity that allows these particles to accumulate and persist in the lungs (IARC, 1997). In humans, it is possible that co-exposure to tobacco smoke and crystalline silica may impair the clearance of these toxic particles (IARC, 2004).